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Possible role of Bronchoscopy in evaluation of Lower Respiratory Tract Infection among Pediatric Population

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Abstract: Background: Lower respiratory tract infection (LRTI) is an inflammation of the airways (pulmonary tissue), due to viral or bacterial infection, below the level of the larynx. LRTI includes various diseases such as: bronchiolitis, wheeze-associated LRTI, bronchopneumonia, Lobar pneumonia and Empyema. LRTI is one of the serious illnesses requiring hospitalization especially in children under 5 years of age. It accounts for 30% of deaths annually worldwide mostly due to pneumonia as the leading cause . In the recent decades, pediatric pulmonology has made significant progress in understanding and managing children's respiratory diseases, and has become a specialty in itself. The advancement of diagnostic tools like flexible bronchoscopy (FOB) has greatly contributed to the development of this speciality. The major advantages of the flexible bronchoscope include the ability to insert it nasally, orally or through a tracheostomy to visualize segmental and subsegmental bronchi in all lung lobes. Flexible bronchoscope is a safe and effective tool for evaluation of children with persistent or recurrent pneumonia, where the underlying diagnosis is not clear from non-invasive diagnostic tests. FOB has also therapeutic role in certain diseases such as a foreign body granuloma by cryotherapy or pulmonary alveolar proteinosis (PAP) by a therapeutic BAL.

Keywords: *Bronchoscopy, Lower Respiratory Tract Infection, Pediatric Population*

Introduction

Lower respiratory tract infection (LRTI) is an inflammation of the airways (pulmonary tissue), due to viral or bacterial infection, below the level of the larynx. LRTI includes various diseases such as: bronchiolitis, wheeze-associated LRTI, bronchopneumonia, Lobar pneumonia and Empyema. LRTI is one of the serious illnesses requiring hospitalization especially in children under 5 years of age. It accounts for 30% of deaths annually worldwide mostly due to pneumonia as the leading cause [1].

Epidemiology

Pneumonia continues to be the biggest killer worldwide of children under five years of age. Although the implementation of safe, effective and affordable interventions has reduced pneumonia mortality from 4 million in 1981 to just over one million in 2013, pneumonia still accounts for nearly one-fifth of childhood deaths worldwide [2].

Furthermore, pneumonia continues to be the leading cause of morbidity for young children outside the neonatal period, particularly in low-and-middle-income countries (LMICs) [3]. Understanding the current epidemiology, and diagnostic and management strategies in these settings may improve preventive, diagnostic and treatment approaches.

Pneumonia is a major problem in children and has been estimated by the World Health Organization (WHO) to occur in around 156 million children (151 million in developing countries and 5 million in developed countries) resulting in 935,000 deaths each year. It has been estimated that Egypt has about 2 million cases of pneumonia every year and 42,000 Egyptian children under 5 years die every year with pneumonia [2]. Around 6% of infants experience at least one episode of pneumonia during the first two years of life [4].

Recurrent pneumonia (RP) is defined as at least two episodes of
pneumonia in one year or three episodes ever, with intercritical radiographic clearing of densities [5].

Sometimes, it is difficult to determine whether pneumonia is persistent or recurrent, unless there has been a symptom-free interval during which chest radiographs have documented clearing of the pneumonia infiltrations [6].

The term non resolving or persistent pneumonia (NRP) has been used to refer to persistence of radiological abnormalities beyond expected time of course [7]. It was also described as the persistence of symptoms and radiographic abnormalities in a LRTI child for over a month, despite a 10-day course of antibiotic therapy [8].

Flexible Fiberoptic Bronchoscopy

In the recent decades, pediatric pulmonology has made significant progress in understanding and managing children's respiratory diseases, and has become a specialty in itself. The advancement of diagnostic tools like flexible bronchoscopy (FOB) has greatly contributed to the development of this speciality [9].

Rigid bronchoscope was in use since 1897 and was primarily used to remove the foreign body from the bronchus and was commonly used only for adults. Since 1967, flexible bronchoscopy has been used in adults and has provided a safer diagnostic and informative approach than rigid bronchoscopy [10].

In 1978, Wood was able to describe a flexible endoscope prototype for pediatric use thanks to the miniaturization of the devices [11]. This instrument has evolved with innovations in the field of fiber optics to allow the exploration of the bronchial tree by video endoscopy at any age, even in premature infants [12].

Detailed bronchoscopic evaluation of airways offers advantages over other diagnostic tools and allows interventional procedures such as biopsy of lesions, removal of foreign bodies, stenosis dilatation and sampling for cytological and microbiological analysis [13].

The major advantages of the flexible bronchoscope include the ability to insert it nasally, orally or through a tracheostomy to visualize segmental and subsegmental bronchi in all lung lobes [14].

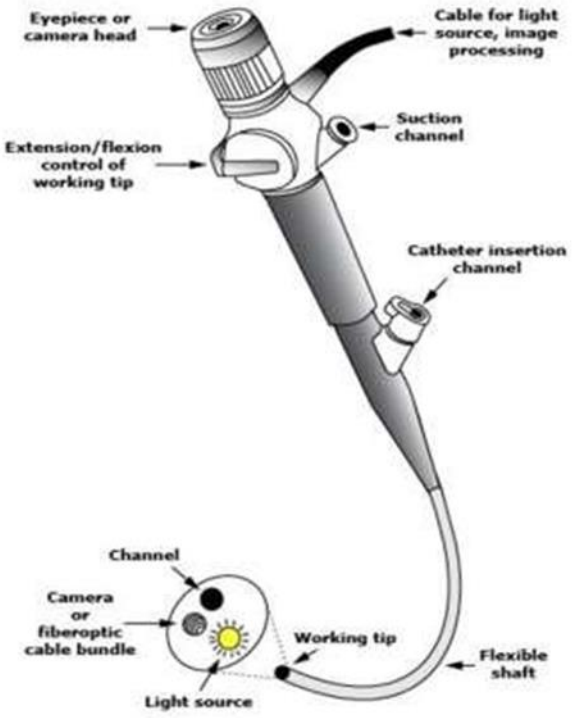
Flexible bronchoscope is a safe and effective tool for evaluation of children with persistent or recurrent pneumonia, where the underlying diagnosis is not clear from non-invasive diagnostic tests [15].On the other hand , it is less effective and less safe in removing bronchial foreign bodies in children compared to adults than rigid bronchoscopy [16].

FOB has also therapeutic role in certain diseases such as a foreign body granuloma by cryotherapy or pulmonary alveolar proteinosis (PAP) by a therapeutic BAL [17].

Components of FOB

The main components of FOB are the following and shown in figure 1

• Eye piece: It can be attached to a camera for display on screen
• Diopter ring for focusing
• Control lever: it controls the tip of bronchoscope. It only permits movement in a vertical plane. Side to side movement is attained by rotation of the body of the bronchoscope with the operator's wrist and shoulder.
• Working channel port: For suction and instillation of drugs .
• Body: Incorporates the eye piece, diopter ring, control level and working channel .It is grasped by the operator non-dominant hand.
• Insertion cord: Contains fiberoptic bundle for light and image transmission, tip bending control wires and working channel.
• Light source: it may be halogen, incandescent or LED.
• Suction valve and port



Figure(1):Components of the flexible bronchoscope [18].

Flexible bronchoscopy procedure

A general protocol is followed to make an FOB procedure,. Six hours fasting was required before the FOB and two after. FOB could be performed in the bronchoscopy unit, an intensive care unit (ICU), or in a surgical operating room [19].
The choice depends on the FOB indication and the patient's clinical condition [20].
It is done under light sedation or under general anesthesia [21].
During the procedure the child can breathe spontaneously around a small FB and under certain conditions, positive pressure ventilation may be required. Ventilation will be also assisted via laryngeal mask, nasopharyngeal or endotracheal tube [22].
Diameters of FOB according to age are listed in table 1

Table (1): Diameters of FOB according to age [23]

Age	Scope size
< 8 years of age	2.8–3.1 mm (1.2 mm suction channel)
8–14 years of age	3.7 mm (1.7 mm suction channel)
> 14 years of age	4.2–4.4 mm (2.0 mm suction channel)
Adults or adult-sized airways	6.2 mm (2.8 mm suction channel)

Airway size	Scope size
ETT: <3.0 mm	2.2 mm (no O_2 or suction capability, only visualization)
ETT: 3.5–4.0 mm	2.8–3.1 mm (1.2 mm suction channel)
ETT: 4.5 mm	3.7 mm (1.7 mm suction channel)
ETT: 5.0–7.5 mm	4.2–4.4 mm (2.0 mm suction channel)
ETT: >8.0 mm	6.2 mm (2.8 mm suction channel)

Abbreviation: ETT – Endotracheal tube.

After crossing the upper airway, the tracheobronchial tree is carefully explored. Then, sampling is performed according to the FOB indication and the bronchoscopic findings. It consists of a BAL, ciliary brushing, and/or bronchial biopsy [24].

Indications of bronchoscopy in pediatrics

Currently, the indications for FOB have widened, making it an inevitable tool in pediatric pulmonology. It is indicated for a diagnostic or therapeutic purpose. It allows direct exploration of the bronchial tree and provides information about its anatomy and the existence of a possible intrinsic or extrinsic obstacle on the airway [25]. Indications of FOB are listed below in table 2

Table (2):Indications of Flexible Fiberoptic Bronchoscopy

Indications	
Diagnostic	**Need for information within the lungs or airways:** • Upper airway obstruction • Chronic cough • Lower airway cultures needed • Abnormal imaging • Localization of bleeding • Severe persistent asthma, difficult to treat • Extubation failure • Biopsies – transbronchial, endobronchial.
Therapeutic	**Need to relieve obstruction in the airways:** • Improve atelectasis due to mucus plugging • Removal of foreign body
Intubation assistance	• Elective, nasotracheal intubation • Difficult view • Spinal issues

Obtaining biological samples through FOB

BAL is the most important aspect of diagnostic bronchoscopy and the best method to obtain specimen from distal airways and alveolar surfaces [10].
Warm saline is installed into distal airways and fluid from the lavage is collected to measure the soluble and cellular contents alveolar surface [26].
In various conditions including chronic interstitial lung diseases, ciliary brushing for electron microscopy analysis in ciliary dyskinesia, and bronchial biopsy in endobronchial masses, the BAL is considered to be important tool [27].
The main indications of BAL are [12]:
 Diagnosis of suspected infection
 Pulmonary infiltrates
 Recurrent and/or persistent pulmonary infiltrates;
 Interstitial infiltrates
 Diffuse alveolar infiltration
 Pulmonary hemorrhage
 Alveolar proteinosis [28]
 Suspected aspiration, Presence of significant number of lipid laden macrophages & Pepsin in BAL samples may support the diagnosis of aspiration.
 Lung transplant , BAL in conjunction with transbronchial biopsy is used to distinguish rejection from infection
 Hyper eosinophilic lung diseases

Technique of BAL

BAL is effectively performed during FOB procedure, contamination of lower airway specimen with upper airway secretions should be avoided. Before the FOB, selection of the site is decided based on clinical, radiologic and bronchoscopic findings. FOB is directed to selected lobe and BAL is obtained from that lobe initially. If there is diffuse disease, BAL can be obtained from multiple lobes especially from lingual and right middle lobe [10].
After identifying the selected lobe, sterile saline is installed through suction channel and 1–2 mL of air is installed to clear the saline from the channel after each aliquot. The temperature of saline can be warmed up to body temperature (37) or keep in room temperature. There is no consensus regarding the number and volume of aliquots that used in BAL. Various protocols have been developed for children. Some bronchoscopists use standard volume of 10-20 mL in 2-4 aliquots regardless of the children's weight and age. Some others adjust the aliquots volume according to body weight [12]. Some suggested that 3 mL/kg of sample into 3 aliquots.In general, 40– 60 percent of the fluid applied is recovered, and the remainder is absorbed. The first aliquot taken is relatively rich in fluid from the surface of the conducting airways and may have higher percentage of inflammatory cells. This sample can be used for cell count whereas remainder samples can be reserved for microbiological analysis [20].

Interpretation of BAL findings

Table (3) Bronchoalveolar lavage (BAL) differential cell counts from different studies of "normal" children [29]:

	Clement *et al.* [78]	Ratjen *et al.* [33]	Riedler *et al.* [19]	Midulla *et al.* [34]	Tessier *et al.* [76]
n	11	48	18	16	11
Age range	1–15	3–5	1#–10	2#–3	4–16
Sedation	LA	GA	GA	LA	LA
No aliquots	6	3	3	2	6
Volume saline	10% FRC	3 mL·kg^{-1}	3 mL·kg^{-1}	20 mL	10% FRC
BAL fluid recovered %					
mean±SD	ND	58±15	ND	43.1±12.2	69.7±9.6
median	ND	ND	62.5	42.5	68
range	ND	ND	42.5–71.5*	20–65	52–87
×10^4 cells·mL^{-1}					
mean±SD	25.5±13.6	10.3±11.1	ND	59.9±32.9	35.1±18.4
median	24	7.3	15.5	51	30.5
range	7.0–50.0	0.5–57.1	7.5–25.8*	20–130	9–68
AM %					
mean±SD	89.7±5.2	81.2±12.7	ND	86±7.8	89.9±5.5
median	89	84	91	87	92.5
range	85–97	34.6–94	84.2–94*	71–98	77–98
Lym %					
mean±SD	8.7±4.6	16.2±12.4	ND	8.7±5.8	8.9±5.6
median	10	12.5	7.5	7	8
range	1–17	2–61	4.7–12.8*	2–22	2–22
Neu %					
mean±SD	1.3±0.9	1.9±2.9	ND	5.5±4.8	1.2±1.2
median	1	0.9	1.7	3.5	1
range	0–3	0–17	0.6–3.5*	0–17	0–3
Eos %					
mean±SD	ND	0.4±0.6	ND	0.2±0.3	0
median	ND	0.2	0.2	0	0
range	ND	0–3.6	0–0.3*	0–1	0

Age range is given in years, except where indicated by # where they are given in months. *: First interquartile to third interquartile. LA: local anaesthesia; GA: general anaesthesia; FRC: functional residual capacity; ND: not done; AM: alveolar macrophage; Lym: lymphocyte; Neu: neutrophil; Eos: eosinophil.

Neutrophils in BAL fluids normally represent less than 5% and neutrophil counts can be detected up to 95% in bacterial infections [10]. Less than 25% of neutrophil count is rarely indicates bacterial infection. Aspiration, asthma, cystic fibrosis, acute respiratory disease and alveolitis can be associated with increased neutrophil counts [30].

Alveolar macrophages in BAL fluids are the most common nonepithelial cells and comprise 80–90 percent of cell counts. Lymphocytes are the second most common cells and composing 5– 10% of total cells. Increased counts of lymphocytes are not specific to a disease but are significantly higher in sarcoidosis, tuberculosis infection, interstitial lung disease, hypersensitivity pneumonitis, Pneumocystis jiroveci infection and non-tuberculous mycobacterial infections [12].

Eosinophil count in healthy children composing about (0–1%) and higher in allergic and parasitic diseases. In BAL samples, pneumocystis carinii infection, interstitial lung disease and drug induced lung disease were also elevated [12].

Concentration of more than 100,000 organism/mL of Staph. aureus, Haemophilus influenza and Strept. pneumonia of BAL fluid in association with increased neutrophils are considered as evidence of infection [31]. Absence of neutrophils, bacteria in BAL liquids present contamination rather than infection. [32].

In patients with Langerhans cell histiocytosis, BAL reveals immunostaining for S-100, CD1a, and langerin. The BAL in pulmonary alveolar proteinosis will reveal periodic acid–Schiff stain–positive, diastase resistant

amorphic material. Patients with alveolar hemorrhage will have evidence of hemosiderin-stained macrophages [25].

Contraindications to bronchoscopy

Flexible bronchoscopy is generally well tolerated. The indication for FFB should be individualized. The procedure should only be performed when the benefits outweigh the risks.
The absolute contraindications that impede performing bronchoscopy are severe refractory hypoxemia, hemodynamic instability, uncorrected hemorrhagic diathesis and the lack of authorization for the procedure by the parent or guardian [33].
The relative contraindications depend on the experience of the team and the level of critical care in the hospital. In very premature newborns and children with congenital cyanotic heart diseases with an increase in bronchial collateral circulation, severe pulmonary hypertension or coagulation alterations, risk-benefit assessment must be done [34].
.

Risks of Flexible Fiberoptic Bronchoscopy

However flexible bronchoscopy has many advantages , it also carries certain risks that are inherent with any medical procedures. Thus flexible bronchoscopy is not free from risks [35]. Complications may occur immediately after the fiber-optic bronchoscope introduction as it interferes with basic respiratory physiological phenomena [36].
FOB has to be performed under general anesthesia and hence risk related to general anesthesia cannot be overlooked upon though it is becoming safer day by day.
Complications depend on risk factors related to the patient, anesthesia procedures, inappropriate choice of the endoscope size and the operator's experience [20].
The main complications of FOB [10]:
1.Nasal trauma and epistaxis
2.Desaturation and hypoxemia
3.Cough and bronchospasm
4.Trauma and obstruction of airway due to edema
5.Hemorrhage
6.Pneumothorax
7.Fever and infections
Fever was the most common reported complication especially if BAL had been carried out during the procedure [37]. It is related with cytokine release or with the transitory bacteremia [12].

Biofilm detection in BAL

Definition :

A biofilm is a collection of microorganisms organized in a matrix of extracellular polymeric material. Biofilms consist of microbial cells that attach to both surfaces and each other, whether they are living or non-living. These microbial biofilms can lead to hospital-acquired infections and are generally detrimental. They possess the ability to resist the human immune system and antibiotics. The National Institute of Health (NIH) states that biofilm formation is associated with 65% of all microbial illnesses and 80% of chronic illnesses.

Additionally, non-device-related microbial biofilm infections include conditions like cystic fibrosis, otitis media, infective endocarditis, and chronic inflammatory disorders [38].

Value & Clinical importance

It was mentioned that almost 80% of chronic infections in animals and humans are associated with biofilm formation [39].
By 2050, the death of 10 million people is expected due to increased rates of morbidity and mortality because of infections caused by MDR pathogens that are the outcome of the misuse of antibiotics together with chronic biofilm-related infections [40].
Persistent biofilm-related infections pose a clinical threat in terms of the morbidity and mortality rates of patients and healthcare-associated costs. Microbial biofilms in hospital settings can be produced in the hospital wastewater, solid surfaces, and medical devices [41]. It is noteworthy to mention that device-related infections with a biofilm aetiology were the first clinical infections to be recognized [38].
Several biofilm-related infections such as foreign body-located blood stream infections due to central venous catheter, ventilator-associated pneumonia due to endotracheal tubes, foreign body-located chronic wounds due to soft tissue implants, tissue-located sinusitis due to cystic fibrosis, chronic urinary tract infections due to urinary tract catheterization, and foreign body-located infection due to drainage associated infections have been recognized in the clinical settings , examples of common pathogens that are involved in the biofilm-related infections are Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacteriaceae, coagulase-negative staphylococci, Acinetobacter spp. and Enterococcus spp. [42].
Additionally, the establishment of biofilms will consequently lead to tolerance to both immune system by shielding the embedded microbes even in the presence of both innate and adaptive immune response and tolerance to antimicrobials which necessitates elevated concentrations of antibiotics administered for a longer period, resulting in chronic persistent infections.
Accordingly, the implementation of new antimicrobial strategies to eradicate microbial biofilms as natural products such as phytochemicals and antimicrobial peptides will facilitate the tackling of biofilm-related infections [43]. These natural compounds possess a broad spectrum of activity, are more stable, reliable, and less liable to produce resistance, and may be subjected to chemical modification to achieve better pharmacological and pharmacokinetic properties. Many studies have worked on bioactive compounds from medicinal plants for finding novel natural compounds that act on biofilms with very promising results [44].
Unfortunately, not a single FDA-approved drug was manufactured even with this huge work. The solution might be the combination of natural agents together with antibiotics to achieve an inhibitory effect on biofilms [45].

Microbial biofilms associated with chronic infections

Chronic infections progress more slowly than acute infections, and they frequently have ambiguous signs. With antibiotics, they are extremely challenging to treat. An acquired inflammatory response, which is predominately composed of IgG antibodies and mononuclear leucocytes, is typically what distinguishes chronic inflammation. A persistent inflammatory response and ongoing recruitment of polymorphonuclear leucocytes are features of the inflammatory response in several chronic infections (PMNs). Before the discovery of antibiotics, the most common chronic illnesses were leprosy and tuberculosis, which steadily deteriorated the tissue and damaged the organs (such as the lungs) of patients before causing death [38].
Chronic infections caused by multidrug-resistant (MDR) pathogens present a great challenge for eradication due to their resistance to conventional antibiotics, as well as their ability to form biofilms and persistence over time. Furthermore, these infections can also influence the host's immune response [46].

Patients with illnesses or disorders that impair the principal protective barriers are susceptible to developing chronic infections (innate immunity). The inflammatory anatomical and physiological barriers, such as the skin, mucous membranes and cilia, as well as phagocytic abnormalities, are all affected by this (e.g. PMNs and macrophages). [47].

Biofilms: challenges in antibiotic treatment

Antimicrobial resistance mechanisms can be categorized into four primary groups:
(1) restricting the entry of a drug.
(2) modifying the target of a drug.
(3) rendering a drug inactive.
(4) actively expelling a drug from the cell.
The specific mechanisms utilized by Gram-negative bacteria and Gram-positive bacteria exhibit variations due to differences in their structures and other factors. Gram-negative bacteria employ all four major resistance mechanisms, whereas Gram-positive bacteria less frequently employ strategies to limit drug uptake (as they lack an outer membrane composed of lipopolysaccharides) and may have limitations in certain types of drug efflux mechanisms (Fig. 2) [48].

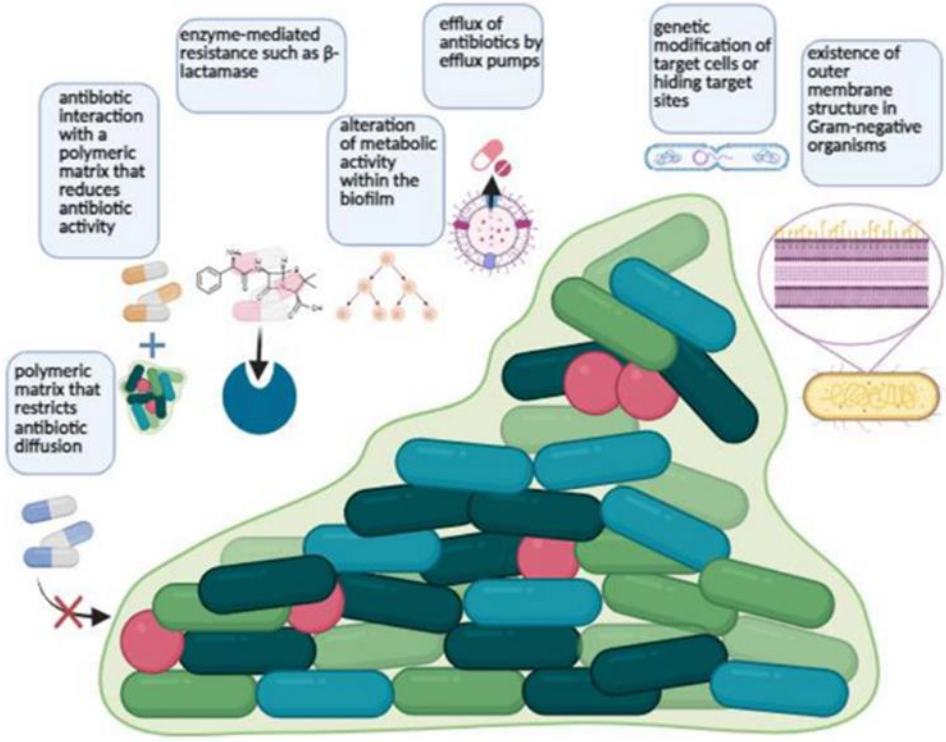


Figure (2): Cartoon representation of biofilm-mediated antibiotic resistance mechanisms [48].
It is well known that microbes demonstrating a biofilm phenotype are difficult to manage and their response to antimicrobial therapy is challenging. Consequently, the biofilm development and the resistance to antimicrobial treatment is quietly related [39].
The management of microbial resistance is threatened by three main conditions: increase of persistent biofilm-related infections, expansion of antimicrobial resistance and the lack of appropriate therapy [49].

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