Respiratory Medicine
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Samuel Goldfarb
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Diagnostic and Interventional Bronchoscopy in Children

Humana Press

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Diagnostic and Interventional Bronchoscopy in Children

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ISSN 2197-7372 ISSN 2197-7380 (electronic)
Respiratory Medicine
ISBN 978-3-030-54923-7 ISBN 978-3-030-54924-4 (eBook)
https://doi.org/10.1007/978-3-030-54924-4

This Humana imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Over the past century, the role of bronchoscopy has evolved from removal of airway foreign bodies by Chevalier Jackson to image-guided precision lung tissue sampling by robotic techniques. This book serves as a comprehensive review of pediatric flexible bronchoscopy fundamentals and as an introduction to the full spectrum of advanced diagnostic and interventional techniques. It represents the collective experience of international experts sharing their insight with the next generation of pediatric bronchologists.

Flexible bronchoscopy has become an indispensable tool used by pediatric pulmonologists to evaluate airway pathology and for select therapeutic interventions. It is exciting to think about where the field will be in the next 5–10 years and beyond. The indications for flexible bronchoscopy in adults have expanded due to major advances in technology. Minimally invasive techniques for targeting lesions in the lung and mediastinum using endobronchial ultrasound (EBUS), computed tomography and electromagnetic navigation have become standard in adult interventional pulmonology programs. As these techniques improve, they have the potential to eliminate the need for surgical biopsy of lung and mediastinal tissue.

Pediatric pulmonologists are now tasked with determining how these tools can be applied to the care of children. Early reports have demonstrated safety and feasibility, but there will be limited opportunity for training and maintenance of skills in the pediatric setting until indications have expanded to provide suitable procedure volumes. Children who could benefit from these procedures include those with thoracic malignancy, immunocompromised pneumonia and radiographic changes of unknown etiology. The greatest potential for increasing the number of children who can benefit from these minimally invasive approaches comes not from advances in the bronchoscopy tools themselves, but from innovation in laboratory analyses. Identification of disease-specific biomarkers and use of genomic technology for microbial detection and cancer diagnostics will maximize the yield of increasingly smaller specimens obtained through image-guided tissue sampling. Only then will the field be ready to make its next leap forward. As we stand on the shoulders of the giants who came before us and who impart their wisdom through this textbook, we can see a bright future and look to the next generation to deliver us there.

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Part I

History and Fundamentals of Flexible Bronchoscopy

1 Pediatric Bronchoscopy: A Personal Odyssey Through 5 Decades

Robert E. Wood

Bronchoscopy – the direct, visual examination of the airways – had its beginning around the turn of the nineteenth and twentieth centuries. Over the next several decades, great advances were made in the understanding of airway pathology and therapeutics, despite the relatively primitive optical characteristics of the available instruments. Pediatric applications, however, were limited almost entirely to the removal of aspirated foreign bodies, and a large variety of very ingenious forceps were designed for specific types of foreign bodies.

The development of the class rod telescope in the late 1960s brought a quantum leap to bronchoscopic technology, enabling detailed visualization and photography. The era of diagnostic bronchoscopy in pediatric patients had begun [1, 2]. However, bronchoscopy was almost exclusively the domain of surgical specialists (and pediatric pulmonology was not yet a defined specialty).

In 1968, Ikeda introduced a flexible fiberoptic bronchoscope, which was initially intended to be used as a flexible telescope passed through a rigid bronchoscope. Soon, however, an intrepid pulmonary fellow described the use of this new instrument by transnasal passage [3], obviating the need for both general anesthesia and the rigid bronchoscope, and the use of flexible bronchoscopes exploded. This generated considerable controversy between the adult pulmonologists and their surgical colleagues [4], but this controversy slowly died out, and flexible bronchoscopy became an integral part of adult pulmonary practice.

I saw my first pediatric bronchoscopy in 1970 – for foreign body extraction – and was not impressed. In 1972, while at the NIH, I saw my first flexible bronchoscopy (in an adult CF patient), and was stunned by the potential of this instrument for research. Shortly thereafter, I discovered that the Radiology department had purchased a flexible bronchoscope, intending to use it for bronchograms, but after using it a couple times had decided not to use it again. I asked, and soon found myself the proud owner of a flexible bronchoscope (6 mm in diameter). With naïve enthusiasm, I learned to use the flexible bronchoscope, essentially having to teach myself. At that time, there was some interest in "therapeutic lung lavage" with a bronchoscope in CF patients [5]. Thinking I could do it better, I performed vigorous procedures with saline mixed with antibiotics in a number of adolescent and young adult CF patients. After several years, I concluded that there was no significant clinical benefit to warrant the procedure.

A more significant event, however, was the seminar by Dr. Marvin Sackner, who described the measurement of tracheal mucociliary transport (and its stimulation by administration of terbuta-

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*,
Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_1

line) by observations through a flexible bronchoscope. I asked him to help me do such a study in CF patients. He sent his colleague, Dr. Adam Wanner, and together we studied 20 patients. The publication of that study [6] enabled me to start my subsequent fellowship at Rainbow Babies and Children's Hospital as the PI of an NIH grant. Although I could show that beta agonists did indeed stimulate mucociliary transport in CF patients, I could not show significant clinical benefit.

Shortly after I began my fellowship, I discovered that the Olympus Corp had marketed a flexible bronchoscope that was only 3.7 mm OD, and obtained one. Without a suction channel, this instrument had limited utility. After some thought, and experimentation, I attached Teflon tubing to the outside of the bronchoscope, and was able to do clinically useful bronchoscopy in children as young as 18 months [7]. With this experience in hand, I approached the Olympus Corp, and asked them to make a flexible bronchoscope suitable for use in children. They were incredulous (at that time, flexible bronchoscopes were primarily used in the management of adults with lung cancer, and they could not imagine why anyone would want to do flexible bronchoscopy in children). Despite their trepidation, in late 1978, I was provided with a prototype, the Olympus BF3C4, based on the specifications I had provided. Overnight, my life changed, and suddenly, I was performing several hundred diagnostic and therapeutic bronchoscopies in infants and children each year.

The advent of pediatric flexible bronchoscopy, like that in adult practice, was not without controversy. In the spring of 1980, I presented my experience in children younger than 6 years at a national meeting (at that time the conventional wisdom was that flexible bronchoscopes could not be used in children younger than 13 years). Despite the obvious diagnostic and therapeutic benefit, with no significant complications [8], I was promptly accused of "medical voyeurism" and "the grossest of medical malpractice for doing this in children." Fortunately, I was not intimidated.

When the first pediatric flexible bronchoscope was marketed, in 1980, a good friend, Bettina Hillman, invited herself to come to Cleveland and be trained by me. She brought a friend, Michelle Cloutier, and I gave those two very nice ladies two weeks of my life. They promptly went home and called all their friends, and I soon realized I could very easily be overwhelmed. I conjured up the idea that if I could get "everyone" to come at the same time, I could give some formal lectures, do some hands-on labs, and then I would never have to do it again – as everyone who needed training would have been trained. Heh, heh, heh… The first course was in 1981 – this year (2020) will mark the 40th year of the course – much expanded in scope and detail, with the addition of rigid instruments. I plan for the course to continue well into the future, in the capable hands of my younger colleagues. The course has been the source of enormous personal satisfaction to me, enabling several thousand physicians to gain a comprehensive introduction to pediatric bronchology and bronchoscopy and to begin to develop their skills.

During the next several decades, the use of flexible bronchoscopy spread widely, and has become an indispensable aspect of pediatric pulmonary practice [9], as well as a useful research tool. Bronchoscopy had a unifying influence on pulmonary practice, enabling practitioners to visualize, sample, and treat the airways of children in ways never before possible. I believe (without evidence, however) that it played a role in the crystallization of the specialty of pediatric pulmonology itself, which became a recognized specialty in 1986. Several important developments occurred along the way to the present day: the introduction of new instruments (smaller diameters, better optics, etc.), more widespread acceptance and "legitimacy" in the eyes of our surgical colleagues, and awareness that in many pediatric patients, the use of *both* rigid and flexible instruments in the same session is extremely valuable.

No sooner had the BF3C4 gone on the market, than I began to press the Olympus Corp to build smaller instruments. The tracheal diameter of a full-term newborn infant is approximately 5 mm, so the 3.7 mm instrument obstructs most of the airway. While it is quite feasible to use this size instrument in premature infants, it must be done the way porcupines make love: extremely care-

fully, and very rapidly. I assisted Olympus in the development of smaller instruments, without suction channels, which are essential to pediatric practice, but much less useful due to lack of suction, eventually leading to the now standard 2.8 mm instrument with 1.2 mm channel. Smaller channels, we discovered, were useless. I believe that we have now reached the practical limits of physics, and that instruments smaller than 2.8 with 1.2 mm suction channel would not add to clinical utility. Unfortunately for me, all my assistance to Olympus has been given *gratis*.

Pediatric flexible bronchoscopy developed essentially independently from advances in rigid instrumentation and practice. Most pediatric flexible bronchoscopists viewed their surgical colleagues as adjuncts, to be called in for special occasions, such as foreign body extraction. Until 1989, I had no access to a pediatric otolaryngologist, and when I did, we did not do concurrent bronchoscopic procedures. It was only when I came to Cincinnati Children's Hospital (CCHMC), in late 1999, to help establish the Aerodigestive Program, that I began to have first-hand exposure to rigid bronchoscopy in real time. It was an eye-opening experience for me as well as for my surgical colleagues. We had each thought that our instruments were "superior" for most applications (although I had always insisted that foreign body extraction was the near-total domain of rigid instruments). We were shocked to begin to discover our own limitations, and the advantages of the other. At CCHMC, rigid bronchoscopy is performed with light anesthesia, spontaneous breathing, and in almost all cases with the glass rod telescope alone, instead of with deep anesthesia and a ventilating bronchoscope. My surgical colleagues, led by Dr. Robin Cotton, thought that they were seeing the upper airway with great fidelity. The very first procedure I did with Dr. Cotton was in a 13-year-old girl with OSA (obstructive sleep apnea). He examined the child first, and saw marked arytenoid prolapse. As he and his fellow were discussing a supraglottoplasty, I discovered that the child also had massive adenoidal hypertrophy, and severe glossoptosis. Both these lesions, each of which could have caused the OSA, had been missed by the rigid laryngoscopy. To Dr. Cotton's everlasting credit, it took him about 5 seconds to change his viewpoint 180°. And I had thought that a laryngoesophageal (LE) cleft was the rarest of pediatric airway anomalies. I did not realize that it is almost impossible to define many LE clefts with a flexible instrument; at CCHMC we make this diagnosis several times each week, in children with histories of recurrent pneumonia, etc. I learned that the posterior glottis and subglottis is the most difficult part of the pediatric airway to evaluate with flexible instruments. In the evaluation of any child with suspected aspiration, examination with *both* rigid and flexible instruments is indispensable.

As a result of our working together, watching each other performing the procedures, my surgical and pulmonary colleagues have established a practice in which at least 2/3 of the more than 2000 flexible bronchoscopies performed each year by the pulmonary group are done in conjunction with ENT as a combined rigid/flexible examination. This is of course very heavily influenced by our patient population, which is dominated by children with complex airway issues. With the flexible bronchoscope, we can observe airway dynamics, unaltered by the mechanical distortion introduced by the laryngoscope and by the rigid bronchoscope itself, and examine and sample the distal airways. With rigid instruments, we can see the fine details of the structure of the larynx and trachea, and manipulate the tissues under direct visualization. In our patient population, 1 + 1 = 3. There are, of course, many patients in whom one or the other type of instrument is most suitable for the immediate need, and in these patients, dual procedures are not performed. In general, *airway dynamics* are best evaluated with a flexible instrument, while the *anatomy* of the larynx, especially the posterior aspect of the larynx, and the cervical trachea, are best evaluated with rigid instruments. It is, for example, very easy to fail to discern posterior glottic stenosis with a flexible instrument, and attribute the endoscopic findings to vocal cord paralysis.

Over the years, I have performed bronchoscopy for many different indications, and have come to recognize that it is useless to make a list of "indications for bronchoscopy" and instead can boil my list down to a single point: Diagnostic bronchoscopy is indicated when there is informa-

tion in the lungs or airways of the child, necessary for the care of the child, and best obtained with the bronchoscope. Likewise, therapeutic bronchoscopy is indicated when bronchoscopy is the most effective way to achieve the therapeutic goal. Bronchoscopy should not be performed if the risk exceeds the potential benefit, but it is important to recognize that many times the most important finding is the definitive exclusion of serious pathology. A normal examination, performed carefully, can yield enormous parental comfort and eliminate other, often more invasive, evaluations.

During my career, I have learned much about the pediatric airways, and about bronchoscopy. For the first half of my career, I had no (or little) access to the services of an anesthesiologist, and performed my procedures with topical anesthesia alone (in teenagers and young adults) or with sedation I administered. I believed that proceduralist administered sedation was superior to anesthesia, and I was wrong. For many reasons. First of all, bronchoscopist's hypnosis is a real phenomenon – it is easy to focus on the procedure and forget about the patient's status. An anesthesiologist's sole responsibility is to maintain the patient in a safe condition, while facilitating the task of the bronchoscopist, who in turn is free to focus exclusively on the airways and the procedure. The drugs available to the anesthesiologist are vastly superior to those available to the pulmonologist, enabling rapid induction and emergence, and safe and effective titration of the level of sedation appropriate to the needs of the bronchoscopist. The anesthesiologist's team takes responsibility for the preoperative management of the patient, and for recovery, freeing the bronchoscopist to do other tasks or to shorten turnover time between cases. The downsides of this approach, however, include higher cost and the fact that the anesthesiologist must recognize the special needs of the flexible bronchoscopist, and cooperate fully. There must be very effective and trusting communication and cooperation between the bronchoscopist and the anesthesiologist. In too many institutions today, the anesthesiologist insists that flexible bronchoscopy be performed with deep sedation/anesthesia, assisted ventilation, and via a laryngeal mask airway (LMA) or endotracheal tube (ETT) (both of which lead to many erroneous diagnoses, by masking/bypassing the upper airway and altering the lower airway dynamics). When I first came to CCHMC, it was the "rule" that all flexible bronchoscopies had to be done via LMA or ETT. Neither the anesthesiologists, nor the otolaryngologists understood the important role of the flexible bronchoscope in the native upper airway. Today, a relatively "new" procedure "Drug Induced Sleep Endoscopy," essentially does what pediatric pulmonologists have been doing for years in every patient – paying attention to the anatomy and dynamics of the upper airway. When I came to CCHMC, a transient desaturation was cause for termination of the procedure, regardless of whether the goals of the procedure had been achieved. There was period of education, demonstration, negotiation, and accommodation before we became a unified team; this is one of the larger challenges facing flexible bronchoscopists in many other institutions, even today, I believe.

I am often asked by a pediatric pulmonologist to provide training in "interventional bronchoscopy." I feel strongly that in the vast majority of cases, this is not indicated. Interventional bronchoscopy includes such procedures as the placement of stents (very rarely indicated in pediatric patients, despite the intuitive appeal in patients with severe dynamic airway collapse), balloon dilation, laser, cautery, cryotherapy, etc. Unless these procedures are done frequently enough to gain *and maintain* competence, they are dangerous. A fool with a tool is still a fool… My pulmonary colleagues and I together perform more than 2000 flexible bronchoscopies per year, and the number of procedures we do that would be classified as "interventional" is less than 25, spread among our six primary bronchoscopists. We have the world's largest pediatric airway surgery program, of which we are a part, and our ENT colleagues do the vast majority of the (still small numbers) "interventional" procedures. I feel strongly that while diagnostic flexible bronchoscopy should be a part of virtually every sizeable pediatric pulmonary program, there should be a greased chute to the most appropriate center of excellence with experience and qualifications to

handle the patients who need "interventional" procedures. One skill that is absolutely critical, however, is the ability to perform a bronchoscopic intubation in patients with critical airways or in an emergency situation. In patients above the age of 10 years or so, an adult interventional bronchoscopist should be able to meet the needs of the patient, but for younger children, a specialized pediatric facility is best. The pediatric airways are (and should be) a frightening place for an adult bronchoscopist without special pediatric training and experience.

Training bronchoscopists has been a significant aspect of my career. I am often asked "how many flexible bronchoscopies must one do to gain competence?" There is no answer to this. I have had fellows who in their third year could not reliably get through the nasal airway and others who within a couple of weeks on the bronchoscopy service develop an amazing level of manual skill with the bronchoscope. At CCHMC, our pediatric pulmonary fellows perform 300–400 or more procedures during their training. But preparation for independent practice involves more than learning how to make the bronchoscope go from point A to point B… Of all the skills of the bronchoscopist, cognitive skills are probably the most important. There are many, many ways to get the wrong answer when doing a bronchoscopy, and experience is by far the best teacher. "What am I looking for," "what am I looking at," and "now, what do I do with it" are questions one is more likely to be able to answer after hundreds of procedures… At a minimum, the aspiring bronchoscopist must be able to know the anatomy (and its normal variants), be able to drive the bronchoscope effectively and safely, be able to recognize the common pathologic findings, and be capable of either dealing with them effectively or of enlisting appropriate consultants in a timely fashion. Bronchoscopy is *not* a "See one, Do one, Teach one" matter…

I do not anticipate that the near future will bring quantum changes in bronchoscopic technology for pediatric patients. The biggest change I anticipate is the development of smaller video chips to improve the optical quality of the images.

What I have learned over the past 5 decades can be summarized briefly:

1. "WNL" all too often *really* means "We Never Looked." The great grandfather of bronchoscopy Chevalier Jackson said, in 1915, "If in doubt as to whether to do a bronchoscopy, you should do the bronchoscopy." That advice is valid today.
2. You never know what you may find in the airways of a child. Even today, I am often very surprised by what I discover.
3. You must do enough procedures to develop and maintain skill. If you are not doing at least one a week, you are unlikely to develop and maintain skill (and you are likely depriving a number of your patients of the potential benefit).
4. Pediatric bronchoscopy is a Team Effort – you must have the proper venue, equipment, and support team for safe and effective bronchoscopy.
5. Wherever pediatric flexible bronchoscopy is done, there must be colleagues skilled and equipped for pediatric rigid bronchoscopy.
6. Effective and timely communication is crucial to safety and success.
7. In order to achieve the correct diagnostic impression, issues relating to sedation and airway management are paramount.

Robert Frost, in his poem "The Secret," said "We dance around in a circle and suppose. But the Secret sits in the middle and Knows." I like to paraphrase this: "We dance around the patient, and suppose. But the bronchoscope sees into the patient, and knows…."

References

1. Benjamin B. Atlas of pediatric endoscopy. Upper respiratory tract and oesophagus. Oxford: Oxford University Press; 1981.
2. Szekely E, Farkas E. Pediatric Bronchology. Baltimore: University Park Press; 1978.
3. Smiddy JF, Ruth WE, Kergy GR, Renz LE, Raucher C. Flexible fiberoptic bronchoscope. Ann Intern Med. 1971;75:971–2.
4. Tucker GF, Olsen AM, Andrews AH Jr, Pool JL. The flexible fiberscope in bronchoscopic perspective. Chest. 1973;64:149–50.

5. Altman RP, Kulczycki LL, Randolph JG, McClenathan JE. Bronchoscopy and bronchial lavage (BBL) in children with cystic fibrosis. J Pediatr Surg. 1973;8:809–14.
6. Wood RE, Wanner A, Hirsch J, Farrell PM. Tracheal mucociliary transport in patients with cystic fibrosis and its stimulation by terbutaline. Am Rev Respir Dis. 1975;111:733–8.
7. Wood RE, Fink RJ. Applications of flexible fiberoptic bronchoscopes in infants and children. Chest. 1978;73:737–40.
8. Wood RE, Sherman JM. Pediatric flexible bronchoscopy. Ann Otol Rhinol Laryngol. 1980;89:414–6.
9. Faro A, Wood RE, Schechter MS, Leong AB, Wittkugel E, Abode K, Chmiel JF, Daines C, Davis S, Eber E, Huddleston C, Kilbaugh T, Kurland G, Midulla F, Molter D, Montgomery GS, Retsch-Bogart G, Rutter MJ, Visner G, Walczak SA, Ferkol TW, Michelson PH. Official American Thoracic Society technical standards: flexible airway endoscopy in children. American Thoracic Society ad hoc committee on flexible airway endoscopy in children. Am J Respir Crit Care Med. 2015;191:1066–80.

2 Organizing and Maintaining a Flexible Bronchoscopy Program

Robert E. Wood

A pediatric flexible bronchoscopy program is a complex operation, and requires a team, not merely one person. In order to justify the base costs to set up to do pediatric bronchoscopy, a certain volume of business is needed, and the bronchoscopist must pay attention to business matters.

The Team

A bronchoscopy team consists of (at least) the following:

- Bronchoscopist(s) – physician(s)
- Assistant(s) for procedures – nurse, respiratory therapist
- Anesthesiologist/sedation nurse – physician/nurse
- Scheduling/clerical/billing staff
- Cleaning staff

The composition of the team will be different in different institutions, but the tasks/roles above must be performed by someone with skill, training, and support to do the job properly. The bronchoscopist is the team leader, and must be aware of and should be personally competent to perform all the tasks of each of the team members. For example, the physician must be knowledgeable about how to clean the bronchoscopes after procedures, and be willing to perform this task when necessary. *The team leader will have a difficult time supervising what he does not know how to do.*

Bronchoscopy is rarely done in a vacuum, and flexible bronchoscopists need to have colleagues who are skilled (and equipped) to do rigid bronchoscopy when the situation demands. Flexible bronchoscopists need to develop and maintain close collegial relationships with their surgical colleagues. Depending on the specific indication for the procedure, it may be important that *both* rigid and flexible instruments are employed during the same procedure (this is especially true for laryngeal lesions, where rigid instruments give a superior image of the structure, but flexible instruments yield a superior evaluation of *dynamics*.

Assistants for bronchoscopy need to be trained and skilled for the task. To draft a willing but untrained nurse or medical student to assist at a procedure is an invitation to disaster, be it damage to the equipment, mishandling of a specimen, or something worse. The assistant's first responsibility is to the patient, although the precise roles played by the assistants before, during, and following the procedures will vary from institution to institution and from situation to situation.

Patients must be safe and comfortable during procedures, and for pediatric patients, this almost always means sedation/anesthesia.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_2

Someone other than the bronchoscopist must be responsible for the safe and effective sedation and monitoring of the patient. This can be a sedation nurse, working under the supervision of the bronchoscopist, or it can be an anesthesiologist. This person's sole responsibility is to monitor the patient and the response to sedation, as well as record keeping (charting medications given, vital signs, etc.). It is useful to note that not just any anesthesiologist will do, as pediatric bronchoscopy is particularly challenging to every basic concept held dear by anesthesiologists (control of the airway, etc.). *There must be clear and effective communication between the bronchoscopist and the anesthesiologist before, during, and after the procedure.* Use of the wrong type or level of sedation/anesthesia or the wrong technique for airway management during the procedure may well lead to an incorrect diagnosis.

Patients do not magically appear – they must be scheduled. The efficiency and style with which patients are scheduled can have a dramatic impact on the success or failure of a program. Procedures must be scheduled with care to take into account other procedures, needs, etc. When feasible, multiple procedures can be scheduled for the same anesthesia session; this requires skillful coordination among services.

Scheduling is more complex than merely picking a date and a time and telling the patient when and where to appear. The scheduler must take into account the availability of the venue, staff, coordination with other services, the urgency of the procedure, the wishes and schedule of the patient/family, etc. Someone must ensure that the patient will be properly prepared for the procedure. This task can be shared among the physician, who sees the patient in advance of the procedure and obtains the informed consent; the nurse, who makes sure that the family understands such matters as when to stop feeding the child, and where and when to appear; and the scheduler, who provides the family with written materials to help them prepare.

Nursing input into patient preparation is important. At CCHMC, families are contacted by phone in advance of the scheduled procedure, after the physician visit, if the nurse did not see the patient at the time of the physician visit. It is a fact of life that nurses, contacting the family after the patient has seen the physician, can often obtain important information that the physician did not. This may be because some parents feel less intimidated by a nurse than a physician, because they may later remember facts not recalled during the physician visit, or for other reasons. The nurse should review risk factors, including specific medical history, behavioral history, medication history, allergies, etc. My personal patients are prescreened by my nurses prior to the initial visit, which allows me to be more prepared for the visit. In patients in whom there are perceived risk factors for anesthesia, a formal anesthesia consult is obtained in advance of the procedure.

The work product of endoscopy is information – images, observations, and their interpretation, as well as test results on specimens obtained during the procedures. The physician must prepare a formal report of the procedure, which is then distributed to the appropriate caregivers (referring physicians, consultants, etc.) and to the medical record. If referring physicians do not receive timely and informative reports, they will have much less incentive or desire to refer patients in the future. While it is the responsibility of the physician to prepare the procedure note, the nursing and clerical staff play an important role in the distribution of the reports and other data. They may also help deliver information to the families.

Finally, bronchoscopy cannot be performed without appropriate instruments that are suitable for use in the patient. Someone, be it the physician, the nurse or RT assistant, or someone specially trained for the task, must be responsible for cleaning the instruments after each use. Another fact of life is that in most institutions, people hired for roles such as this are not college graduates, and may not be highly motivated by intellectual goals. It is important to carefully train, supervise, and encourage staff who care for the instruments. They can make or break the program. In their own way, the role (and the responsibility) of the instrument cleaners is as important as is the role of the physician.

The Venue

Bronchoscopy must be performed in an appropriate venue. The venue must be safe, and it must be effective for the purpose. Flexible bronchoscopy *could*, in theory, be performed almost anywhere (on a city bus, an airplane, an operating room), but what *can* be done is not necessarily what *should* be done. There are three basic venues for bronchoscopic procedures: operating rooms, endoscopy suites, and intensive care units.

An *operating room* is almost always an appropriate venue, especially when an anesthesiologist is employed to assist with the sedation of the patient. There may be challenges in scheduling, and one cannot be certain (without prior evaluation and arrangement) that the proper/necessary equipment and supplies are available in the OR. Depending on the acuity of the patient's problem, the complexity of the intended procedure, and the anticipated need for other services, the OR may be the only logical place for the procedure.

An *endoscopy suite* is an ideal venue for many bronchoscopic procedures. The suite must be fully equipped for any foreseeable emergency (hemorrhage, pneumothorax, cardiac arrest, etc.). Unless there is a "critical mass" of procedure numbers, staffing may be a problem. In many institutions, an endoscopy suite can be shared among several services (i.e., pediatric and adult pulmonology, or pediatric pulmonology and pediatric gastroenterology, etc). This will result in more efficient utilization of resources, including equipment (light sources, video processors, procedure tables, etc.), but may result in some difficulties due to scheduling conflicts. Properly administered and operated, however, an endoscopy suite that includes pediatric flexible bronchoscopy can be among the most cost-effective units in a hospital.

It is technically possible to perform flexible bronchoscopy at the patient's bedside. This makes it tempting to "have scope, will travel…" and to perform procedures just about anywhere. However, *this is unwise in the extreme*, and *it is rarely safe or effective to do bedside procedures outside an intensive care unit*. Even in an ICU, the bronchoscopist must ensure that appropriately trained staff are available to assist. Not any ICU nurse will be an effective bronchoscopy assistant, especially when the patient is unstable. On the other hand, for many patients, the ICU is an ideal venue, if moving the patient to another facility involves risk or very serious inconvenience. When procedures are done in the ICU, the bronchoscopist must ensure that everything that could possibly be needed comes along to the ICU. This includes such simple things as slip-tip syringes (not usually available in ICU's – the standard Luer-lock syringes will not work with flexible bronchoscopes).

Preoperative and Patient Recovery Facilities

Many pediatric flexible bronchoscopies are performed on an outpatient basis, and there must be an appropriate venue for the patient prior to the procedure. Sharing an outpatient surgery facility with surgical services can be very cost effective. Likewise, the patient must have a safe and effective venue for postoperative recovery from sedation, and it is very effective to share the post anesthesia recovery unit with surgical services. The most dangerous time for a patient undergoing bronchoscopy may be immediately after the procedure is completed; with no further stimulation, the patient may become apneic, and the staff tend to relax their vigilance once the procedure is completed.

Equipment

It has been said that the difference between men and boys is the price of their toys. Flexible bronchoscopists must be *real* men, because our toys are *very* expensive (with all due apologies to the women who are also very good flexible bronchoscopists). A pediatric flexible bronchoscope costs on the order of $25,000. It is difficult to operate a meaningful pediatric bronchoscopy program with only one instrument. At a *minimum*, I recommend the following:

- 2–2.8 mm flexible bronchoscopes
- 1 adult bronchoscope (available; possibly borrowed on an ad hoc basis from the adult services) with 2.0 mm suction channel
- 1–2.2 mm flexible bronchoscope (this instrument has no suction channel, and is therefore of relatively limited utility, but when it is needed, nothing else will do)
- 1 light source
- 1 video processor
- 1 monitor
- 1 video recording system

It can be cost effective (especially when sharing an endoscopy suite) to share the light sources, video processors, monitors, and video recording systems. I strongly recommend, however, that the 2.8 mm flexible bronchoscopes not be shared with other services, as they are not robust, and are very easily damaged by users not accustomed to these small instruments (no matter how otherwise skilled or well-meaning). The half-life of a flexible bronchoscope in the hands of a gorilla (i.e., anyone untrained or irresponsible) is approximately 17 milliseconds.

The light source, video processor, etc., should be mounted on a cart so it can be moved from site to site. There also needs to be a cart with all the supplies and ancillary equipment that would be needed at another venue (i.e., ICU); the video monitor can be mounted on this cart, which can then be positioned appropriately for best visibility during the procedure.

Equipment Cleaning

Next to performing the procedure, cleaning the equipment is the most important aspect of bronchoscopy. An improperly cleaned bronchoscope can be lethal. There is only one criterion for a clean bronchoscope – it is ready to be used on the bronchoscopist. After the procedure is completed, the soiled instrument must be carefully transported to the cleaning facility. This step is a critical one, for it is here that many instruments are physically damaged. Care must be taken to avoid contamination of the clean environment by a dirty instrument. A cleaning facility must be capable of maintaining effective separation between dirty and clean equipment, of properly cleaning and then disinfecting the instruments, and storing them appropriately.

Equipment Storage

It is important to have a secure place to store equipment. The cost of a flexible bronchoscope exceeds $25,000, and theft or vandalism (intentional or otherwise) can wreak havoc on a bronchoscopy program's operations (not to mention the budget). Storage should not only be secure, but should ensure that the equipment is kept clean and ready for use on short notice. The hospital's Infection Control staff should be involved in decisions about instrument storage.

Handling the Data Generated by the Procedures

The job is not done until the paperwork is done. A sad fact of life is that often what we write seems more important than what we've done. But *the work product of endoscopy is information* – images, observations and their interpretation, and data generated from specimens obtained during the procedure.

Image management – I believe that all procedures should be recorded whenever possible. I have had the miserable experience of reviewing a video recording of a procedure done as long as a year previously, and finding a very significant abnormality that I missed during the procedure itself. I have also been an expert witness in legal cases that I believe would never have become a legal case had the procedure been recorded.

Bronchoscopy generates large volumes of images, whether still images or video recordings, and it is important to have a systematic way to retrieve the images when they are needed. A computerized database of procedures, with information about the image storage (e.g., videotape number, DVD number) is virtually mandatory. There are systems now available for the central recording and archiving of video data, which

make the results of endoscopic procedures readily available for review at multiple locations as needed. At CCHMC, all endoscopic procedures since 2006 are recorded in an online video archive, and can be accessed very quickly.

Images obtained during bronchoscopy are useful not only for the medical record, but for teaching medical professionals and for education of patients and families. Still images can be incorporated into procedure notes. It may be very helpful to show parts of the video record to parents or even the patient, to help them understand the findings and their significance.

Procedure reports are an important part of the medical record, and, sadly, in our current medicolegal atmosphere, are perhaps the most important aspect of the procedure. They are used for many purposes, including patient management, teaching, research, and as support documentation for reimbursement. The report needs to include the indications for the procedure in the context of a brief history, a description of the procedure and the findings, the complications, diagnostic impressions, and a discussion and plan for follow-up. It can be helpful to incorporate photos into the report, although this requires special editing and cannot readily be done through centralized hospital dictation systems. There are software packages available that can help generate a report and incorporate photos.

Procedure reports need to be distributed to the appropriate places, including the medical record, the referring physician and other physicians participating in the care of the patient, etc. While the report should, in general, be prepared as soon after the procedure as possible, in many cases it may be advantageous to defer preparation of the final version of the report until data from the BAL specimen (cultures, cytology) are available and can be incorporated into the final impressions and recommendations. If not, then care must be taken to ensure that the data do not disappear into the ether, and that appropriate action is taken in response to the findings.

Handling specimens – other than death of the patient, the most serious complication of bronchoscopy is to do the procedure and get the wrong (or no) answer. One of the most common mistakes that can lead to a wrong answer is mishandling of the specimens (BAL, biopsy, etc.). The bronchoscopist must be sure that the laboratory knows how to process the specimen in the most appropriate way, and that the laboratory understands what information is needed and how to report the data. It does the patient no good to entrust the BAL specimen to a courier who leaves it sitting on a desk while he takes a break, only to have the specimen (finally) arrive after the laboratory has closed for the night. What then happens to it? BAL specimens need to arrive in the microbiology laboratory within an hour after collection, and should be processed promptly. It does the patient no good if the biopsy specimen is placed into the wrong preservative, or if the wrong tests are requested on the requisition. The bronchoscopist should pay careful personal attention to the laboratory requisitions, making sure that all the important information is recorded properly*, and if necessary, carry the specimen to the laboratory himself.*

Communication

The name of the game is effective communication. The bronchoscopist must communicate with the team members in a timely and effective manner (and vice versa). It is very important to achieve effective communication with the patient/family prior to the procedure. Setting the proper expectations can be critically important to patient and family satisfaction, regardless of the diagnostic findings of the bronchoscopy. There needs to be effective and timely communication with the family afterwards, as well. If the family expects to receive the results of the BAL cultures but has no idea of the time frame, they may call the physician's office three times a day. If, however, they are told ahead of time that it will take 4–5 days for the information to become available, many unnecessary phone calls, wasted time, and considerable angst can be avoided.

Communication among professionals is also of critical importance. First of all, for proper patient care, the physician(s) responsible for the patient need to have the information gained by

the procedure. Secondly, bronchoscopy is primarily a referral service, and without a steady flow of patient referrals, the bronchoscopy program will not support itself. Satisfied customers (aka referring physicians) will be repeat customers.

Business Matters

Business matters *matter*. Someone, if not the bronchoscopist, must pay careful attention to billing for procedures, setting appropriate charges, accounting for expenses and revenue, etc. While many patients' medical needs are covered by insurance, you can be certain that insurance companies will take every excuse not to pay for your services (this is another reason careful documentation is so important). The documentation must support the charges submitted, and the procedure coding must be appropriate. In the United States, CPT codes are required for billing. The current code for a diagnostic bronchoscopy is 31622; if bronchoalveolar lavage is also performed, the code is 31624. It is not appropriate to utilize *both* (and to charge for) 31622 and 31624 on the same procedure by the same physician. Likewise, it is usually (although not always) considered inappropriate to bill for both a diagnostic bronchoscopy 31622/4 *and* a laryngoscopy (31575). The rules for procedural coding can be complex, may change from year to year, and the bronchoscopist should learn to use them most effectively. In any case, the bronchoscopist must be prepared to back up the billing with a procedure note, which documents the indications, procedure, findings, and plan.

Reimbursement for procedures is always an unsettling process for physicians. No matter how we charge for our services, third-party payers will attempt to reduce the payments. It is important to track billings and receipts, to investigate and follow up on denials, and to adjust practices to ensure that the maximum fair payments are received. In general, there will be two components to the charges for a bronchoscopy: the professional fee, and the facility fee. Generally, the facility fee is managed by the institution, and should be structured to include the costs of the equipment, supplies, staff, procedure room, etc.

Capital equipment costs for flexible bronchoscopy can be significant. As noted above, sharing resources with other services that use the same light sources, video processors, etc., can be very cost-effective. At current prices, a flexible bronchoscope costs approximately $25,000, a light source $14,000, a video processor $24,000. Thus the cost to set up even a relatively modest program can exceed $75,000. This can seem like a major investment on the part of the institution. However, the global revenue to the institution generated by a flexible bronchoscopy program far exceeds the direct costs attributable to the procedures themselves. There are radiology studies, clinic visits, hospital admissions, OR charges, and laboratory fees, as well as additional services directly or indirectly resulting from the patient referral (i.e., other surgical procedures, ICU stays, etc.). These revenues constitute a hidden "multiplier factor," which hospital administrators use to evaluate the potential impact of a program. Only the administrators know the factor the institution uses in its considerations, but you can be assured that the numbers are larger than you might suspect. Be aware of this when you negotiate with the institution for support of your program.

Equipment repairs can be a major headache, especially if there is no service contract. The cost of a service contract will depend on a number of factors, including your track record with the equipment supplier, the number and type of instruments you have, etc. The cost to replace a fiberoptic bundle in a flexible bronchoscope is on the order of $10,000; it is easy to see why a contract is a good idea. Flexible bronchoscopes can last for years if they are cared for in a proper fashion, but can be broken in milliseconds if not. When an instrument must be sent for service, it is important to have a replacement instrument for patient care. While a "loaner" instrument may be available from the manufacturer, this is not always the case, and I strongly recommend that you have a minimum of two instruments. If you are not doing enough procedures to justify having

two, you are probably not doing enough procedures to justify doing any. ☹

The economics of a flexible bronchoscopy program can be complex. However, it can be a source of significant revenue, not only from the procedures themselves, but also from cost savings (early diagnosis leading to decreased ICU stays, for example), and can lead to increased patient referrals to the institution. In building a business plan with your institution, consider all potential revenue, and plan for expansion. In my 20 years at Cincinnati Children's Hospital, the number of flexible bronchoscopies performed by pulmonologists increased from approximately 100/year to more than 2200 in 2019. A rather sizeable impact.

The road to success

1. Build, train, and nurture your team.
2. Ensure that you have a proper venue.
3. Obtain and maintain proper equipment.
4. Handle data (images, reports, specimens) properly.
5. Maintain good records – a database is essential.
6. Have a good business plan.
7. Work with your institution for mutual support.
8. Communicate.
9. Communicate.
10. Communicate.
11. Build and nurture collegial relations within your institution.
12. Build and nurture collegial relations with referring physicians and institutions.
13. Pay close attention to business matters.
14. Have fun!

References

1. Rayhorn N. Sedating and monitoring pediatric patients. Defining the nurse's responsibilities from preparation through recovery. MCN Am J Matern Child Nurs. 1998;23:76–85.
2. Blair KC. Sedation and hypnoanalgesia in pediatric endoscopy. SGA J. 1988;10:230–3.
3. Committee on Drugs, American Academy of Pediatrics. Guidelines for the elective use of conscious sedation, deep sedation, and general anesthesia in pediatric patients. Pediatrics. 1992;89:1110–5.
4. Kociela VL. Pediatric flexible bronchoscopy under conscious sedation: nursing considerations for preparation and monitoring. J Pediatr Nurs. 1998;13:343–8.
5. Schmitt S. Nursing aspects of flexible bronchoscopy in premature and newborn infants. Kinderkrankenschwester. 1996;15:450–5. (in German)
6. Welsh S, Myre L, Gatch G. Pediatric bronchoscopy. Special considerations. AORN J. 1987;46:864–8.
7. Manna SS, Durward A, Moganasundram S, Tibby SM, Murdoch IA. Retrospective evaluation of a paediatric intensivist-led flexible bronchoscopy service. Intensive Care Med. 2006;32:2026–33.

3 Upper Airway Anatomy and Physiology

Conor Devine and Karen Zur

Nasal Cavity

The nasal cavity extends from the anterior nasal aperture to the beginning of the nasopharynx posteriorly and is divided into two separate cavities by the nasal septum. Broadly speaking, the nasal cavity has three key functions: respiration, protection, and olfaction. An average adult human inhales 10,000 L of air daily [1]. The upper airway has evolved to allow for both oral and nasal breathing, but in the absence of nasal obstruction, humans preferentially rely on the nasal airway for respiration. The large surface area of the sinonasal cavity has superior heat and moisture exchange capabilities, and is adapted to trapping impurities in inhaled air. The nasal cavity accounts for approximately half of total airway resistance—significantly greater than that of the oral cavity [2]. The nasal cavity accounts for the largest and greatest fluctuation in resistance to airflow; however, these fluctuations are not made as quickly as in other segments of the upper airway, such as the pharynx, oral cavity, and larynx [2]. Unlike these other segments of the upper airway, the nasal cavity is largely immobile save the contribution of facial mimetic musculature to flare nostrils and dilate the nasal valve. Rather, changes in nasal airflow are largely mediated by the autonomic control of the robust mucoperiosteal lining of the nasal cavity.

Anatomy

The external nose is pyramidal in shape, reflecting the paired nasal bones, paired upper lateral cartilages, and paired lower lateral cartilages supported in the midline by the nasal septum. The bony framework of the nasal cavity is comprised of several bones of the skull and midface. The lateral walls of the nasal cavity consist of the maxillary bones and lacrimal bones. The palatal processes of the maxilla and the horizontal processes of palatine bones form the floor, which is the nasal surface of the hard palate. And the roof of the nasal cavity has contributions from the cribriform plate, the ethmoid bones, the sphenoid bones, the nasal bones, and the frontal bones. The anterior bony entrance to the nasal cavity is called the pyriform aperture and is a heart-shaped opening formed by the nasal bones and maxillary bones. The external nasal opening or nostril is formed by the nasal ala, the nasal sill inferiorly, and the nasal columella medially. The columella is formed by the medial crura of the lower lateral cartilages. The nostril gives way to the nasal vestibule, which is lined with stratified squamous

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_3

epithelium and houses hairs called vibrissae, which trap large particles in inspired air [3, 4]. From here, the nasal cavity extends posteriorly to the nasal choana or posterior nasal aperture. This space marks the boundary between the nasal cavity and the nasopharynx. It is bounded by the vomer, the sphenoid bones, the medial pterygoid plates, and the palatine bones (Figs. 3.1 and 3.2).

The midline nasal septum divides the nasal cavity into two separate cavities, thereby helping to increase surface area of the nasal cavity. In addition to dividing the airway, it provides structural support to the nasal dorsum and serves as one of the primary sources of nasal tip support. The nasal septum is divided into three segments: the membranous septum, the cartilaginous septum, and the bony septum. The membranous septum extends from the columella to the quadrangular cartilage where the cartilaginous septum begins. The quadrangular cartilage attaches superiorly to the perpendicular plate of the ethmoid bone, posteriorly to the vomer, and inferiorly to the maxillary crest of the maxilla. Here it is firmly adherent to the maxilla by way of decussating fibers which help to anchor it. Posterior to the quadrangular cartilage, the perpendicular plate of the ethmoid descends from the skull base to meet the vomer inferiorly and form the bony septum [4–6].

The septal perichondrium and periosteum carry rich vascularity to the overlying respiratory epithelium from the internal and external carotid artery systems via the ophthalmic, maxillary, and facial arteries. This robust vascularity has significant contributions to the physiology of the nasal airway, helping to regulate nasal airflow, heat exchange, and humidification. During endoscopic evaluation, one may notice the bilateral septal swell bodies on the anterior septum, just anterior to the level of the middle turbinate. While these may look like septal deviations, they are areas of thickened mucosa which are soft and compressible [7].

Along the lateral nasal wall are bony outcroppings called conchae. These form the bony scaffold for the respiratory epithelium-covered turbinates, which are fully developed by 24 weeks gestation [8]. The superior and middle turbinates stem from the ethmoid bone while the inferior turbinates originate from the maxilla. The primary purpose of the turbinates is to greatly increase the surface area of the nasal cavity to aid in humidification, heat exchange, and filtration. The inferior turbinate is the largest of the three with most robust

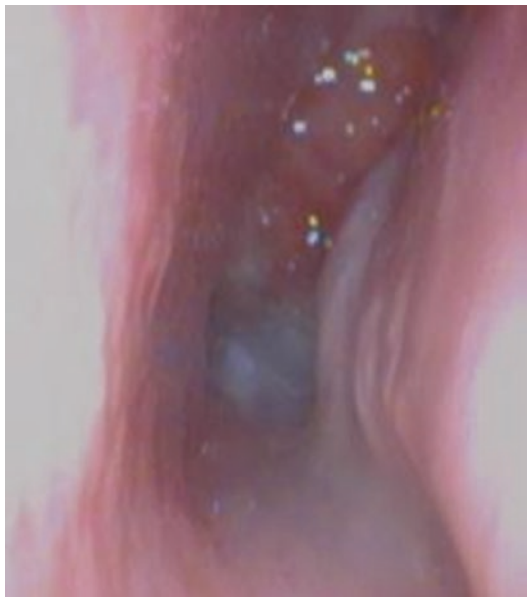

Fig. 3.1 Left choana showing partial obstruction by adenoid bed superiorly

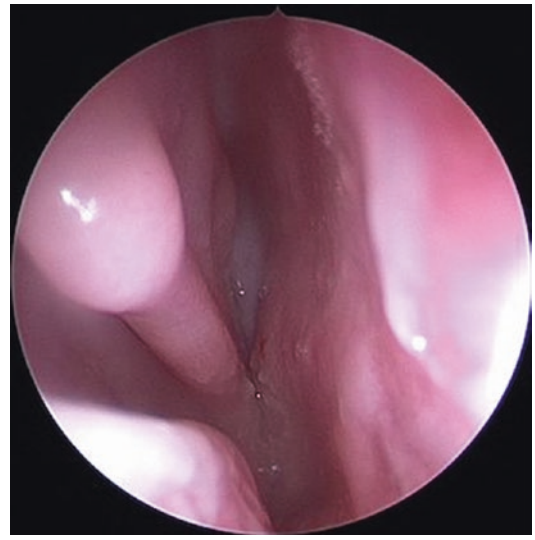

Fig. 3.2 Right choanal atresia. Notice the posterior septal deviation and blind-ended cavity

mucosal erectile tissue. This, in addition to its association with the nasal valve, makes it a major contributor to nasal obstruction and nasal airflow resistance. The spaces beneath the turbinates are referred to a meati and serve as drainage passages for mucocilliary clearance. The nasolacrimal duct drains anteriorly into the inferior meatus, channeling tears posteriorly into the nasopharynx. The middle meatus which is found beneath the middle turbinate, receives drainage from the maxillary sinus, frontal sinus, and anterior ethmoid sinuses. Obstruction of this region, which is often referred to as the ostiomeatal complex, leads to build up of mucus, infection, and sinusitis. Finally, the superior meatus receives drainage from the posterior ethmoid air cells [4]. When passing an endoscope through an adult nasal cavity, it is often most spacious along the floor of the nose; however, due to the relative sizes of the inferior turbinate and the nasal cavity of a child, it is often easier to pass through the middle meatus.

The blood supply to the nasal cavity is supplied by both internal and external carotid systems. The terminal branches of the external carotid system, which supply the nasal cavity, include the superior labial arteries off the facial artery, and the sphenopalatine, descending palatine, and infraorbital arteries off the internal maxillary arteries. The anterior and posterior ethmoid arteries are branches off the ophthalmic arteries from the interal carotid system. These two vessels descend from the skull base to supply the nasal septum. Temperature, pain, and touch sensation to the internal and external nose is provided by the first two divisions of the trigeminal nerve. However, olfaction is a function of the specialized olfactory bulbs of the first cranial nerve. Except for the keratinizing squamous cell epithelium of the nasal vestibule and the specialized lining of the olfactory cleft, the mucosa of the nasal cavity is pseudostratified, ciliated columnar epithelium.

Physiology

Nasal Cycle

Patients frequently report a fluctuating or alternating nasal obstruction. Indeed asymmetric nasal congestion and edema can often be seen on both physical exam and radiographic studies. This is the result of the normal nasal cycle, which is present in approximately anywhere from 20% to 80% of the population. The term nasal cycle is used to describe the asymmetric and occasionally periodic fluctuations in venous congestion of the venous sinuses along the nasal septum and inferior turbinates. With engorgement of the venous sinuses, the mucosal lining swells resulting in increased nasal airflow resistance. The typical nasal cycle takes anywhere between 30 min and 3 h to complete [3, 9–11]. Though the side of the nasal cavity experiencing the mucosal swelling experiences an overall increase in nasal obstruction, the total nasal airflow resistance remains stable throughout [10]. In patients with preexisting anatomic asymmetry of the nasal cavities, this phenomenon may lead to what is referred to as "paradoxical nasal obstruction," where the side that is perceived to be obstructed due to cyclic swelling may be more patent than the permanently narrowed side. In patients with a fixed anatomic asymmetry like a deviated septum, the total nasal resistance fluctuates depending on mucosal swelling.

Nasal Valve

The nasal valve is perhaps the most significant segment of the nasal cavity for understanding nasal airflow. The nasal septum forms the medial wall of the internal nasal valve. It is also bound by the upper lateral cartilages and head of the inferior turbinate laterally, and the nasal floor inferiorly (Fig. 3.3). The angle between the septum and upper lateral cartilages is typically cited as 10 to 15 degrees. Derangements in this angle have significant implications for airway patency. As the narrowest segment of the nasal airway, the nasal valve has the most significant control over nasal airflow and the greatest contribution to airflow resistance [3, 5, 6, 12]. Poiseuille's law helps to explain the dramatic effect even a small change in the cross sectional diameter of the internal nasal valve has on nasal airflow, as the airflow through the nasal cavity is proportional to the radius of the airway to the fourth power [12].

Inspired air enters the nasal cavity through the nasal vestibule and then is channeled through the

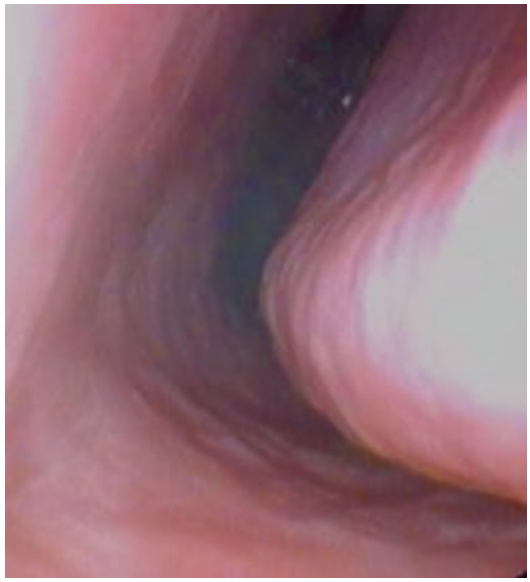

Fig. 3.3 Left nasal passage demonstrating the region of the nasal valve bordered by the nasal septum (left), the inferior turbinate (right), and the nasal floor

nasal valve where its flow is laminar. Air accelerates through the nasal valve reaching speeds of up to 18 m/s, and then upon reaching the turbinated nasal airway, airflow slows down to 2 m/s and becomes turbulent, allowing greater interaction with the nasal sidewall, turbinates, and septum [1, 3, 4, 12]. Turbulent airflow through the nose is critical for all major functions of the nasal cavity because it ensures more of the inspired air comes in contact with the turbinated nasal airway. By the time inspired air enters the nasopharynx, it has reached 37 degrees Celsius and approximately 85% humidity [13, 14]. Foreign particles have been filtered out of the air because turbulent airflow provides greater opportunity for inspired particles to become trapped in the mucous lining. Finally, greater turbulence ensures more airflow past olfactory epithelium.

A common reason for narrowed nasal valve is septal deviation. Nasal septal deviation may be present in anywhere from 75% to 90% of the population [8]. One explanation for this high prevalence may be deviation secondary to facial trauma during passage through the birth canal. Whatever the cause, a deviated septum can significantly reduce the angle of the nasal valve and result in dramatically increased resistance to nasal airflow. When septal deviation involves the quadrilateral cartilage, it may be evident as a resulting deflection of the external nasal dorsum. While a septal deviation at the level of the nasal valve may dramatically narrow the nasal airway, a posterior deviation involving the vomer in the posterior nasal cavity may have relatively little impact on airflow. Likewise, the endoscopist may find passing a flexible scope through the nasal passage difficult with an anterior deviation, but have relatively little difficulty with a posterior deviation.

Another common reason for nasal obstruction and narrowing of the nasal valve is turbinate hypertrophy. As was previously discussed, the nasal cycle leads to alternating nasal congestion. This is a repetitive and physiologically normal process which resolves at the completion of the cycle. However, turbinates are also commonly enlarged in the presence of allergy and vasomotor rhinitis. In these conditions, the sinusoids within the mucoperiosteum become engorged, leading to significant soft tissue swelling. The resultant edema reduces the cross sectional diameter of the nasal valve. On evaluation with fiberoptic scopes, engorged turbinates will often appear boggy and erythematous. This fullness may be accompanied by thin rhinorrhea. The swelling is soft and can often be pushed past with the telescope; however, application of topical decongestants such as oxymetazoline will greatly reduce this swelling by inducing vasoconstriction. While septal deviation is often perceived as ipsilateral nasal obstruction, a "paradoxical nasal obstruction" may occur due to contralateral turbinate hypertrophy. Unlike the edema seen in allergic rhinitis, the turbinate hypertrophy which accompanies deviated nasal septum is often bony in nature as well. In this case, it may be much more difficult for the nasal valve to accommodate a bronchoscope.

Allergic rhinitis is a common cause for alterations in nasal airflow. This IgE mediated hypersensitivity of the nasal lining is more common in children than in adults and has a strong familial predisposition. When an inhaled allergen lands on the nasal mucosa, it is engulfed by macrophages, dendritic cells, or Langerhans cells and

then through a series of immunologic signaling pathways, IL-4, IL-5, and IL-13 incite the production of IgE. Upon re-exposure to the antigen, an IgE-mediated release of inflammatory substances from mast cells results in the symptoms of allergic rhinitis. The swelling that results to cause nasal obstruction associated with allergic rhinitis is predominantly localized on the nasal septum and inferior turbinates [15, 16].

During sleep, as in wakefulness, humans are preferential nasal breathers. Despite evidence that recumbency causes nasal congestion in the ipsilateral nasal cavity as the gravity-dependent side, there is no significant change in total nasal airway resistance from wake to sleep [13]. The nasal cycle persists independent of posture, and the physiology of the nasal airway does not undergo the same derangements as the pharynx during sleep [17]. Oral breathing during sleep bypasses any nasal airway reflexes which participate in maintaining airway patency. In addition, with oral breathing, the mandible is displaced inferiorly and posteriorly counteracting actions of the pharyngeal dilators. These factors may contribute to greater incidence of obstructive sleep apnea with mouth breathing.

Mucociliary Clearance

The primary way in which the nasal cavity protects the lower airways is through mucociliary transport. As was previously stated, the lining of the nasal cavity is pseudostratified ciliated columnar epithelium. Goblet cells within the epithelium create a mucus blanket which covers the nasal cavity and traps inspired particles. Surrounding the cilia is a less viscous periciliary sol layer which permits the beating of the cilia. This motion of the cilia propels the thicker overlying gel layer toward the pharynx where it will be swallowed. The more gelatinous surface layer traps particles and also contains various antimicrobial proteins. The health of the mucociliary transport system within the nasal cavity is paramount to maintaining nasal airway patency and preventing disease. Failure of the mucociliary transport system, as seen in diseases like cystic fibrosis can lead to infections, inflammation, and obstruction of the nasal airway [1, 14, 18, 19].

Oral Cavity

Anatomy

The oral cavity begins at the lips and continues posteriorly to where the oropharynx begins at the junction of the hard and soft palate. It is bound superiorly by the hard palate, inferiorly by the floor of mouth, and laterally by the cheeks. The bony framework of the oral cavity is composed of the mandible and the hard palate. The hard palate consists of the palatine processes of the maxilla and the horizontal plates of the palatine bones. Together, they form the U-shaped roof of the oral cavity that separates it from the nasal cavity.

Within the oral cavity, there are several anatomic subsites—the lips, gingivae, teeth, oral tongue, buccal mucosa, floor of mouth, retromolar trigone, and hard palate. Forming the opening to oral cavity, the upper and lower lips meet at the oral commissures laterally. In addition to participating in speech formation and facial expression, the human lips act as a sphincter for mouth closure through action of the orbicularis oris muscle which encircles the mouth. Controlled by the facial nerve, this muscle is responsible for maintaining oral competence during mastication and swallowing. Deep to the buccal mucosa of the cheek, the buccinator muscle works in conjunction with the orbicularis muscle and other muscles of mastication to keep food aligned with the occlusal surfaces of teeth and prevent pockets of food from forming in the cheeks. The space enclosed by the lips, the teeth and alveolar processes, and the buccal mucosa is referred to as the oral vestibule. It is into the lateral oral vestibule that saliva from the parotid duct, or Stensen's duct, empties adjacent to the second maxillary molar.

The maxillary and mandibular alveolar ridges are lined with dense fibroepithelial mucosa, the gingiva. From these ridges arise the teeth whose primary function is to cut and grind food. In children, 20 deciduous emerge and are eventually replaced by 32 permanent teeth. Posterior to the third molars is the retromolar trigone, which occupies the space between the mandibular ramus, maxillary tuberosity, buccal mucosa, and tonsillar pillar.

The hard palate is divided into the primary palate, and secondary palate by the incisive foramen through which the nasopalatine nerve passes. The muscles of the soft palate attach to the posterior edge of the hard palate where the oral cavity merges with the oropharynx. At birth, the hard palate is generally broader and less arched than the adult palate. However, as teeth erupt along the alveolar ridge, the palatal arch deepens. Simultaneously, the oral surface of the palate enlarges while the nasal surface resorbs, and the volume of the nasal cavity increases [20]. In patients with a cleft palate, failure of the two maxillary prominences to fuse in the midline results in an open palate and common oronasal cavity. The hard palate is covered by a thick mucosal layer of keratinized squamous epithelium. Like the mucosa of the rest of the oral cavity, it houses many minor salivary glands which produce mucus to lubricate and prevent drying. The hard palate is supplied by the greater and lesser palatine arteries which pass through the greater and lesser palatine foramina and are branches of the internal maxillary artery.

The dominant structure within the oral cavity is the oral tongue. This occupies the greatest space and significantly contributes to respiration. The oral tongue, also referred to as the mobile tongue, is the anterior two-thirds of the tongue which lies anterior to the sulcus terminalis and circumvallate papillae. The bulk of the oral tongue is made up of 4 paired intrinsic tongue muscles. These include the superior longitudinal, inferior longitudinal, transverse, and vertical muscles. Together, they work to lengthen, shorten, flatten, and round the tongue, and it is through their contraction that the tongue is able to curl and roll. Protrusion, retraction, and changing the tongue position are controlled by the 4 paired extrinsic muscles which originate outside the main body of the tongue but attach to it. These include the primary tongue protruder, the genioglossus, and the styloglossus, hyoglossus, and palatoglossus, which retract the tongue. Each of these muscles is controlled by the hypoglossal nerve except for the palatoglossus, which is innervated by the vagus via the pharyngeal plexus. General sensation to the oral tongue is carried by the trigeminal nerve while taste is carried by the chorda tympani, a branch of the facial nerve. The surface of the tongue is covered with several hundreds of papillae, which house the taste buds responsible for allowing humans to detect sweetness, saltiness, sourness, bitterness, and umami [21]. The lingual arteries, which are branches of the external carotid arteries, supply blood to the tongue muscles. As will be discussed elsewhere in this chapter, in addition to assisting with speech formation, mastication, and swallow, the tongue plays an important role in maintaining airway patency.

Physiology

In addition to the saliva produced by the minor salivary glands within the oral cavity, the mouth receives additional contributions of saliva from the paired parotid, submandibular, and sublingual salivary glands. The largest of the salivary glands, the parotid glands, are located along the mandibular ramus and produce mostly serous saliva, which empties into the oral cavity via Stensen's duct in the buccal mucosa. The submandibular glands are slightly smaller and sit between the digastric muscle and mandible. These glands produce a more viscous saliva, which accounts for about 70% of salivary volume [22]. Submandibular saliva empties into the oral cavity via Wharton's ducts, which run along the floor of mouth before opening at papilla adjacent to the lingual frenulum. Finally, the sublingual glands can be found deep to the mucosa of the floor of mouth, just anterior to the submandibular glands. Adults may produce up to 1.5 L saliva daily which aids to prevent the oral cavity from drying, lubricate food, and initiate digestion. Maintaining a healthy flow of saliva is also crucial for prevention of dental caries and halitosis as saliva helps to regulate oral pH and remove bacteria and bacterial substrates [22]. Salivation is under autonomic control and can be triggered by the presence of food in the oral cavity as well as smell, taste, and even psychological stimuli [23]. During endoscopic evaluation of the airway, taking note of the presence and quality of saliva and

secretions can be an excellent indicator of health or disease status. While dry mucus membranes may be a result of various rheumatologic disease or iatrogenic influence, sialorrhea and pooling of secretions often points to dysphagia.

Like swallowing and breathing, chewing is controlled by central pattern generators (CPG) in the brainstem. CPGs are sensory and motor neuron circuits which coordinate rhythmic events in the body [24, 25]. The process of mastication is beyond the scope of this chapter. However, mastication contributes to the oral phase of deglutition and is essential for facilitating a safe and coordinated swallow, thereby protecting the lower airway from aspiration. The food bolus is mixed with saliva which initiates digestion and lubricates the food to facilitate the swallow. During formation of the bolus, the glossopharyngeal and lingual nerve reflexes help to protect the tongue from inadvertent bite trauma [26]. Once the oral preparatory phase is complete, the tongue elevates and propels the bolus posteriorly toward the oropharynx where the reflexive swallow will begin. This is discussed in greater depth later in this chapter.

At birth, the oral cavity is almost entirely occupied by the tongue, rendering the neonate an obligate nasal breather. This changes as the child grows, and after infancy, the oral cavity becomes a passive conduit for respiration. The nasal airway remains the primary airway; however, during times of heavy activity and with nasal or nasopharyngeal obstruction, mouth breathing predominates. Recall that the resistance to airflow though the oral cavity is much less than through the nasal cavity. While this is true, the oral cavity is not equipped to condition or filter inspired air in the same way that the nasal cavity is. Orally inspired air enters the lower airway cooler and drier than that which is inspired nasally; and oral breathing permits more aerosolized particles into the lower airway. During mouth breathing, the tongue is actively depressed by contraction of the intrinsic muscles and the hyoglossus muscle. This acts to open the pharyngeal airway. Simultaneously, the soft palate is contracted to close of the nasopharynx, worsening the nasal obstruction [27]. An additional physiologic reason for oral breathing is gasp breathing. Triggered by hypoxia, gasp breathing results in protrusion of the tongue by way of genioglossus contraction, which draws the hyoid and tongue anteriorly and opens the pharynx widely to minimal resistance to airflow [21]. With persistent hypoxia, however, research has shown that tongue protrusion fatigues. Thus, in patients with sleep apnea, as hypoxia worsens, so too may their ability to resist worsening pharyngeal collapse [28].

This highlights that perhaps the most important contribution the oral cavity has to upper airway physiology is through the interaction between the tongue and the pharynx. In addition to working toward a safe and coordinated swallow, the tongue musculature also helps to dilate the pharynx. This will be addressed further in the pharynx section. There are myriad anatomic variations and pathologic conditions that may impinge on the oral airway, however the role of endoscopy in their evaluation and diagnosis is fairly minimal. Generally, a direct oral exam using a tongue depressor, dental mirror, and manual palpation is of greater utility than endoscopy.

Pharynx

The pharynx is the largest and most compliant segment of the upper airway. As part of the alimentary and respiratory tracts, it serves as a conduit for both air and ingested food and drink. It is a "space" between the oral cavity and the laryngeal airway. As such, it has two opposing functions—to remain patent during inspiration, and to close and constrict to propel food into the esophagus. Roughly cylindrical in shape, the pharynx works as a muscular channel lined with mucosa that extends from the skull base to the esophageal inlet. In addition to serving as a conduit for ingested food and liquid from the mouth to the esophagus, the pharynx receives and swallows secretions from the nasal cavity and the middle ear. Additionally, the tonsillar tissue of the pharynx is positioned strategically at the portal of entry for air and ingested matter where it comes into contact with myriad antigens, especially

early in life. Though important in the immature immune system, the tonsillar tissue of Waldeyer's ring is more germane to this text for its influence on airway dynamics. Perhaps beyond the scope of this chapter, it is important to recognize the role the pharynx also plays in speech and sound formation, acting as a chamber to increase resonance as well as shape sound generated in the larynx.

At various stages of development, the human pharynx undergoes significant changes both anatomically and physiologically. Prenatally, the developing larynx is positioned high in the neck allowing the epiglottis and soft palate to first interlock at around weeks 23 to 25. When the larynx is high in the neck, the aerodigestive pathway is much like that in other mammals and primates, allowing the neonate to breathe and feed simultaneously. Centrally, a channel is maintained for passage of air, while milk is diverted laterally around the epiglottis, into the pyriform sinuses, then to the esophagus [29]. While this anatomic relationship is intact, the child is an obligate nasal breather. This relationship between larynx and pharynx continues until approximately 2 years of age, at which point the larynx begins its descent in the neck. The pharynx elongates, eventually reaching adult size by about age 6, resulting in the loss of the relationship between the epiglottis and uvula/soft palate [20, 30]. The epiglottis can no longer interlock with the palate, and for the first time, the pharynx is truly a common aerodigestive cavity. It is at this time that the child transitions from obligate nasal breather to being able to rely more on an oral airway when needed [30].

Anatomy: Endoscopic Evaluation

Nasopharynx

In examining the pharynx endoscopically, it is helpful to recall its tripartite configuration. The nasopharynx, oropharynx, and hypopharynx all share certain common anatomy and physiologic functions, but each has a distinct endoscopic appearance. The nasopharynx is the superiormost segment of the pharynx and directly communicates with the nasal cavity via the choanae as well as the middle ear spaces via the Eustachian tubes. The pharyngeal fornix forms the superior extent of the nasopharynx and lies along the occipital and sphenoid bones. Anteriorly, the nasopharynx begins at the choanae. Recall that the choana is the space through which the nasal cavity and nasopharynx communicate. It is bordered by the vomer, the sphenoid bones, the medial pterygoid plates, and the palatine bones. From here, the nasopharynx extends inferiorly to the pharyngeal isthmus—the space between the posterior border of the soft palate and the posterior pharyngeal wall. This marks the boundary between the nasopharynx and oropharynx.

Immediately posterior to the choanae, along the lateral walls of the nasopharynx sit two cartilaginous mounds known as the torus tubarius, which mark the Eustachian tube orifices. These structures serve as the attachment for the salpingopharygneus muscle, which merges inferiorly with the palatopharyngeus and forms the salpingopharyngeal fold. Posterior to this fold sits the fossa of Rosenmuller or pharyngeal recess, which is clinically significant when evaluating for nasopharyngeal carcinoma. Occasionally during routine endoscopic evaluation, a midline smooth, cystic-appearing mass may be observed in the posterior nasopharynx. Known as a Tornwaldt's cyst, this is generally attributed to abnormal notochord regression. Some series have quoted the incidence of these benign growths between 1.4% and 3.3% of the population, though a more recent radiographic study of incidentally found cysts suggested the incidence may be closer to 0.06% [31, 32]. Rarely, these cysts may become infected or grow large enough to cause airway obstruction, but predominantly, they are asymptomatic.

During endoscopic evaluation of the pediatric nasopharynx, one must pay special attention to the pharyngeal tonsil/adenoid bed. Located in the posterior, superior aspect of the nasopharynx, the adenoids comprise part of Waldeyer's ring, lymphoid tissue ideally situated for exposure to both airborne and ingested antigens [33]. Adenoid tissue first develops during gestation and continues to grow through the first 6 years of life after which it generally atrophies and becomes less

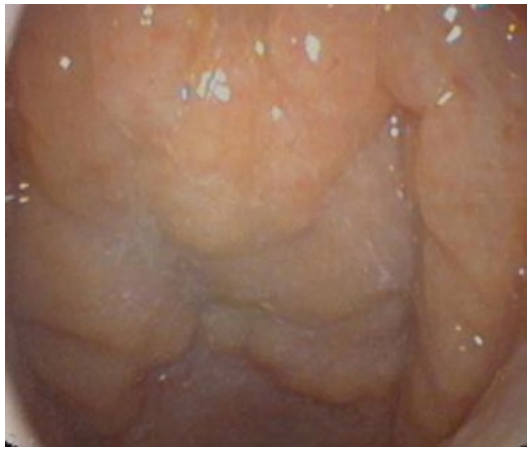

Fig. 3.4 Normal-appearing adenoid bed within nasopharynx

prominent. When hypertrophic, adenoid tissue may significantly obstruct the nasal airway and reduce nasal airflow. Adenoid hypertrophy is marked by symptoms of snoring, nasal obstruction, mouth breathing, and eventually alterations in facial development [34, 35]. Not surprisingly, the presence and degree of nasal obstruction symptoms has been shown to correlate closely with the size of adenoid tissue evaluated endoscopically (Fig. 3.4) [36–39].

The mucosa of the nasopharynx reflects its location between the respiratory epithelium-lined nasal cavity and the stratified squamous epithelium of the rest of the pharynx. Just posterior to the choanae, the mucosa is primarily respiratory, whereas at the level of the pharyngeal isthmus, it has transitioned to stratified squamous epithelium.

Oropharynx

The next segment of the pharynx following the nasopharynx is the oropharynx which communicates with the oral cavity, the nasopharynx, and the hypopharynx. As mentioned above, the oropharynx begins at the pharyngeal isthmus. Anteriorly, the oropharyngeal isthmus or isthmus of fauces encompasses the soft palate, the palatoglossal arches, and the posterior one-third of the tongue. The oropharynx extends from the junction of the hard and soft palate to the level of the hyoid, or the vallecular inferiorly. Within the oropharynx are several subsites that are easily examined endoscopically—the soft palate and uvula, the palatine tonsils, the posterior one-third of the tongue or tongue base, the posterior pharyngeal wall, and the vallecula. Due to the presence of the palatine and lingual tonsils as well as the base of the tongue, the oropharynx is often the source of obstruction in obstructive sleep apnea.

Tonsils

Two of the most significant structures for the endoscopist are the lymphoid collections referred to as palatine and lingual tonsils. The palatine tonsils are secondary lymphoid organs, which arise from the second pharyngeal arch, and can be found between the palatoglossus and palatopharyngeus muscles, bordered laterally by the superior constrictor muscle [33, 40, 41]. Like the adenoids, the tonsils are epithelial lined, highly cryptic structures which comprise part of Waldeyer's ring. Their highly cryptic surface structure maximizes surface area for interaction with antigens. Though the surface of the tonsils is epithelial lined, the crypts are lined with reticular epithelium with large open spaces filled with non-epithelial cells including T cells, immunoglobulin-producing B cells, dendritic cells, and Langerhans cells [40]. The underlying basement membrane is interrupted, allowing for easier delivery of antigen to the lymphoid tissue within the tonsillar tissue. In addition to the lymphoepithelial tissue, tonsils are made up of mantle zones, populated by dense, small lymphocytes; follicular germinal centers, where memory B cells and plasma cells are formed; and interfollicular areas, which are populated predominantly by T-lymphocytes and high endothelial venules which facilitate extravasation.

In palatine tonsils, primary follicles develop by 16 weeks gestation, and by 20 weeks, the crypts have begun to develop and are fully formed by 7 months gestation. Postnatally, tonsillar tissue continues to develop, but by around age 4–7, adenoid tissue has begun to involute, followed by palatine tonsillary tissue by the teenaged years, and finally, lingual tonsils during adulthood [40, 41]. The size and appearance of tonsillar tissue is widely variable in children, as are the ways in which the tissue influences disease status. Not all

hypertrophic tonsils result in sleep apnea or sleep disordered breathing.

Glossoptosis

During respiration, the tongue base is prevented from collapsing posteriorly into the vallecula by contraction of the tongue and cervical strap musculature. Anterior and superior forces on the tongue and hyoid bone help to stent open the pharynx during inspiration, thereby resisting powerful negative inspiratory pressures. Specifically, the genioglossus muscle has been shown to have increased electromyography (EMG) activity during inspiration [42, 43]. Despite this action, certain pathologic conditions result in loss of the oropharyngeal airway. This is especially true in patients with neuromuscular disorders, macroglossia, or micro/retrognathia [44]. Endoscopically, the tongue base may be seen crowding the oropharynx and pushing the epiglottis against the posterior pharyngeal wall, obstructing the airway. In these scenarios, a jaw thrust helps to pull the tongue and hyoid anteriorly, providing a wide open view of the hypopharynx and larynx. This maneuver may be helpful when determining whether or not a mandibular distraction will significantly alter upper airway dynamics.

Hypopharynx

Finally, the oropharynx gives way to the hypopharynx at the level of the epiglottis. The hypopharynx extends down to the posterior surface of the cricoid cartilage and laterally along the lateral surfaces of the larynx into the pyriform sinuses. These mucosa-lined pockets are formed by the aryepiglottic folds medially and the thyroid cartilage laterally. Like the oropharynx, the hypopharynx is lined with stratified squamous epithelium. Though squamous cell carcinoma may originate in the hypopharynx, there are few pathologies that arise here in the pediatric patient. However pooling of secretions observed endoscopically may provide information on the status of the swallow, aspiration, and airway protection.

Drug-Induced Sleep Endoscopy

Over the past several years, drug-induced sleep endoscopy (DISE) has become an important diagnostic tool for sleep doctors and endoscopists. Typically, DISE has been utilized in children who have previously had an adenotonsillectomy but have persistent OSA. By inducing a sleep-like state while evaluating the upper airway, the level of persistent obstruction may be identified [45, 46]. Common sites for obstruction are the velum or soft palate, oropharynx, base of tongue, and epiglottis (VOTE). The first three of these subsites are anatomic components of the pharynx while the epiglottis is part of the larynx. This procedure is also frequently used in patients with high likelihood of having persistent OSA despite adenotonsillectomy, including patients with trisomy 21, craniofacial abnormalities, obesity, and hypotonia. DISE may also help in identifying the site of obstruction in patients with OSA but clinically insignificant tonsils. In these patients, lateral pharyngeal wall collapse is infrequently identified, so adenotonsillectomy may not lead to improvement [47].

Pharyngeal Musculature

The three largest and most prominent pharyngeal muscles are the pharyngeal constrictor muscles, which, when activated, propel food into the esophagus. The superior constrictor muscle attaches superiorly to the skull base at the pharyngeal tubercle anterior to the foramen magnum, the medial pterygoid plate, the pterygomandibular raphe, the mylohyoid line of the mandible, and the lateral tongue. The middle constrictor attaches to the greater and lesser horns of the hyoid bone and the stylohyoid ligament. As it fans out posteriorly, it overlaps with fibers of both the superior and inferior constrictors. Finally, the inferior constrictor muscle attaches to the thyroid cartilage and the lateral aspect of the cricoid cartilage. The inferior constrictor fibers that originate on the cricoid cartilage insert on the circular muscle fibers of the esophagus creating the cricopharyngeus muscle. This muscle forms the upper esophageal sphincter, helping to prevent gastroesophageal reflux and regurgitation of ingested food. Posteriorly, each of the constrictors is attached to the cervical vertebrae in the midline at the pharyngeal raphe which is continuous with the pharyngobasilar

fascia—a dense fascial plane between the mucosa and muscular layer that attaches superiorly to the occipital and temporal bones. Though the pharyngeal constrictors form the cylindrical wall of the pharyngeal lumen, they do not play a role in maintaining patency of the pharynx during respiration. Rather, this task is accomplished by a host of other extrinsic muscles known as pharyngeal dilators, including the genioglossus, geniohyoid, tensor palatine, and anterior belly of the digastric [29, 48].

The three additional paired muscles of the pharynx are the salpingopharyngeus, the stylopharyngeus, and the palatopharyngeus. The salpingopharyngeus originates on the torus tubarius within the nasopharynx and then merges with the palatopharyngeus muscle. When activated, the salpingopharyngeus works to dilate the Eustachian tube opening, allowing for pressure equalization between the middle ear and pharynx. It also assists in elevation of the larynx during deglutition. The palatopharyngeus muscle, covered in mucosa forms the posterior tonsillar pillar, and as the name implies, it originates on the palate and then inserts into the pharynx. Here, it merges with the stylopharyngeus muscle which originates on the styloid process and inserts on the thyroid cartilage and merges with the pharyngeal constrictors. Together, these muscles help to elevate the pharynx and larynx during deglutition, and assist in propelling the food bolus toward the esophagus.

Motor innervation of the pharynx comes from the vagus nerve via the pharyngeal plexus. This is true for all pharyngeal musculature except for stylopharyngeus muscle, which receives motor input from CN IX (glossopharyngeal nerve) [29].

Pharyngeal Physiology

Airway Patency

The physiology of the pharyngeal airway has been studied extensively, especially in its relationship to obstructive sleep apnea [49, 50]. As previously stated, the pharyngeal constrictors have little impact on the maintenance of pharyngeal patency. This is instead accomplished by several extrinsic muscles with pharyngeal attachments referred to as pharyngeal dilators. The two most studied muscles of this group are the genioglossus and tensor veli palatini muscles. These two muscles are the most readily accessible for monitoring and EMG testing. The genioglossus, which attaches to the mandible and inserts on the tongue protrudes the tongue, and when activated during inspiration, it works to pull the posterior portion of the tongue down and anteriorly. This action results in the dilation of the pharyngeal airway. The tensor veli palatini, on the other hand, is innervated by the trigeminal nerve. Extending from the Eustachian tube to wrap around the Hamulus of the medial pterygoid plate and insert on the soft palate, contraction of this muscle dilates the pharyngeal airway at the level of the soft palate, pulling it away from the posterior pharyngeal wall [51, 52].

Much of what has been discerned about the genioglossus and tensor veli palatini contribution to pharyngeal physiology is extrapolated to other extrinsic muscles of the pharynx as well. Not surprisingly, neuromuscular control of the pharyngeal dilators is complex and is controlled by multiple factors including the pre-Boetzinger—a central pattern-generating complex within the brainstem, chemoreceptors, mechanical receptors, and wakefulness stimuli. The pre-Boetzinger complex, which is responsible for rhythmic control of the diaphragm, also provides motor stimulation to the hypoglossal nerve [50]. In both the genioglossus and tensor palatini muscles, there is a sharp decrease in motor activity at the onset of sleep, also referred to as the alpha-theta transition [53]. When the "wakefulness stimuli" that helps to maintain pharyngeal patency is diminished with sleep onset, the pharynx is more susceptible to obstructive collapse. This is implicated in the multifactorial etiology of OSA. Recently, the hypoglossal nerve stimulator has been employed to exploit this relationship, providing rhythmic stimulation to the hypoglossal nerve throughout sleep, thereby mitigating this loss of wakefulness drive [54, 55].

In addition to wakefulness stimuli, there are chemoreceptors within the brain that respond to increasing CO_2 and mechanical receptors that

respond to the negative airway pressure to increase genioglossus activity and increase upper airway tone [56]. This is demonstrated by the negative pressure reflex. With an increase in upper airway resistance, nasal obstruction for example, airflow decreases and the resulting negative pressure beyond the obstruction results in collapse of the pharyngeal airway. This change in pressure is detected by mechanical receptors which trigger the pharyngeal dilators to resist the collapse [50, 57] (Figs. 3.4, 3.5, 3.6, and 3.7).

The prevalence of OSA in children is as high as 1–4%, yet in obese children, this may be as high as 25–40%. In obesity, excess adipose stores build up in the soft tissues of the neck, resulting in smaller cross-sectional area of the pharyngeal airway secondary to extrinsic compression. Additionally, this tissue leads to increased compression during sleep when pharyngeal dilator tone decreases [58, 59].

Swallow

The primary function of the pharyngeal musculature is to participate in the complex process of swallowing. Humans typically swallow around 500 times daily, each swallow employing 30 muscles under the control of multiple cranial and peripheral nerves [24]. While advancing a food bolus from the oral cavity to the esophagus, the pharynx must also work to protect the airway. Breathing and swallowing are both governed by brainstem central pattern generators (CPG)—sensory and motor neuron circuits which coordinate rhythmic events in the body [24, 25, 60]. Communication between these two CPGs leads to coordinated movements of the pharyngeal musculature, tongue, and larynx. The swallow is initiated during the post-inspiration/expiration phase, followed by a brief apnea, and then an expiration. During the brief apnea, the laryngeal adductors are activated to close off the trachea. This sequence of events helps to safeguard against aspiration of food particles into the lower airway [61–63]. In the neonate, however, in

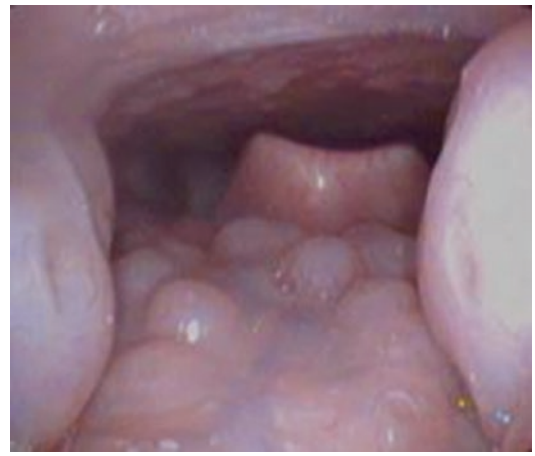

Fig. 3.6 Pharynx with tonsillar hypertrophy causing lateral crowding, and prominent lingual tonsils

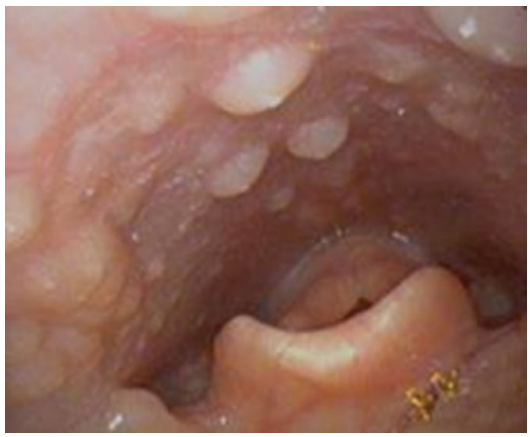

Fig. 3.5 Patent pharynx with cobblestoning of posterior pharyngeal wall

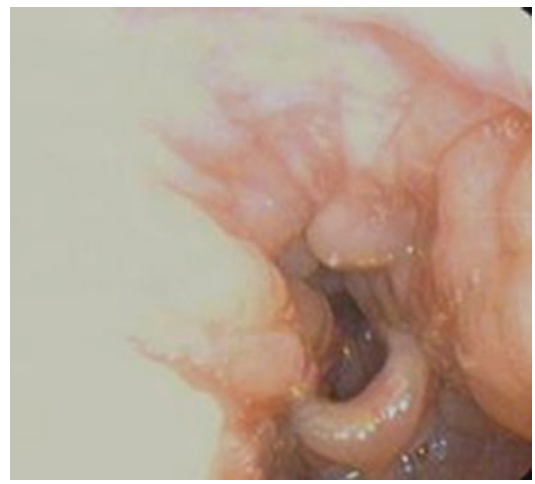

Fig. 3.7 Circumferential pharyngeal collapse

whom the airway is partially protected by its cephalad positioning and the relation between the epiglottis and uvula, this swallow pattern has not been established. Rather, there is a greater tendency to initiate swallow during inspiration [64]. The pharyngeal swallow in the neonate is often not initiated until the presence of a milk bolus in the valleculae [65].

In general, it is helpful to divide the swallow mechanism into four phases: the oral preparatory phase, the oral transit phase, the pharyngeal phase, and the esophageal phase. During the oral preparatory phase, food is chewed and mixed with saliva and salivary amylase, thereby beginning the process of digestion. The food bolus is then formed and positioned on the anterior portion of the oral tongue. Next, the soft palate elevates to contact the posterior pharyngeal wall and close off the nasopharynx and nasal cavity from the oropharynx. Simultaneously, the tongue elevates and pushes the bolus into the oropharynx [27]. This oral transit phase is followed immediately by the pharyngeal phase, which is initiated when the food bolus triggers tactile receptors of the anterior tonsillar pillars [66, 67]. In turn, a "leading complex" is initiated which entails contraction of the genioglossus, mylohyoid, hyoglossus, stylohyoid, and geniohyoid muscles. The end result of the leading complex is hyoid elevation and anterior displacement which draws the larynx up toward the tongue base and causes the epiglottis to retroflex over the larynx [24, 67]. In addition to protecting the lower airway, this anterosuperior displacement of the larynx helps to open the upper esophageal sphincter. In conjunction with a peristaltic pharyngeal wave, a negative pressure gradient is created, and the food bolus is pulled into the esophagus.

The pharyngeal swallow is modulated by several different stimuli detected by oropharyngeal receptors. Upon reaching the anterior tonsillar pillars, the food bolus triggers the swallow reflex [66, 67]. Additional tactile, thermal, and taste receptors within the oropharynx modulate the latency, and strength of the downstream swallow [24, 60]. In neonates, however, the trigger for swallow mechanism may be the accumulation of food in the vallecula rather than passage of food past the pharyngeal arch. Studies have shown that the speed of the pharyngeal swallow increases with age—4-year-old children take statistically significantly longer to swallow a bolus of water than their 12-year-old or adult counterparts [68]. The length of time it takes for the mature pharyngeal swallow to develop speaks to the complexity of the physiologic function and the degree of coordination required to maintain a safe common aerodigestive tract.

Larynx

The human larynx has evolved from a mere sphincter to protect the lower airway to a highly specialized organ with the elegant neuromuscular control required to produce the human voice. At birth, the immature larynx is anatomically optimized for respiration, not unlike our primitive mammalian ancestors. As the child matures, so too do the reflexes facilitating mature feeding, respiratory control, and phonation. This is mirrored by the anatomic position of the larynx. At birth, the larynx is positioned high in the neck with its inferior border at the fourth cervical vertebra. Throughout childhood, the larynx descends in the neck, reaching the level of C6-C7 by about 15 years of age [69, 70]. While this descent increases the length of the pharynx, and exposes the larynx to greater risk of aspiration, it also generates a resonance chamber for vocalization. Simultaneously, the laryngeal framework matures and sexual dimorphism becomes apparent during puberty. By this point, the three functions of the larynx—protection, respiration, and phonation—are fully developed and well-coordinated. This chapter will discuss the anatomy and physiology of the larynx, focusing on important considerations for the bronchoscopist.

Anatomy

Laryngeal Framework

The bony-cartilaginous framework of the larynx is comprised of the hyoid bone, the thyroid, cricoid, epiglottic, and arytenoid cartilages and the

sesamoid cuneiform and corniculate cartilages. The hyoid bone is a horse-shoe-shaped bone suspended from the skull base and the mandible by its many muscular and ligamentous attachments. It is oriented roughly horizontally with its open end facing posteriorly. Directly below the hyoid bone, attached by the thyrohyoid membrane sits the thyroid cartilage. Roughly shield-like, the thyroid cartilage houses the vocal folds, with the anterior commissure attaching to the inner surface of the thyroid cartilage via a dense collection of connective tissue known as Broyle's ligament [71, 72]. The thyroid cartilage is made up of two lamina which meet midline at a 120-degree angle in the infant larynx. During puberty, sexual dimorphism of the adult larynx becomes apparent and this angle becomes closer to 90 degrees in males [70, 73]. Like the hyoid, the thyroid cartilage is open posteriorly, where it attaches to the pharyngeal constrictors. The thyroid cartilage sits just above the signet ring-shaped cricoid cartilage, to which it is attached by the cricothyroid membrane and the cricothyroid joint. This joint allows contraction of the cricothyroid muscle to tilt the cricoid cartilage posteriorly, thereby elongating the vocal folds and changing vocal pitch [74]. Unlike both the hyoid and thyroid cartilage, the cricoid cartilage forms a complete cartilaginous ring. In the neonate, the airway at the level of the cricoid cartilage is the narrowest segment, measuring as narrow as 4–5 mm in diameter [75].

The paired arytenoid cartilages are roughly pyramidal in shape and articulate with the surface of the posterior cricoid cartilage via the ball and socket cricoarytenoid joints. All intrinsic laryngeal muscles, save the cricothyroid muscle, attach to the arytenoid cartilages, and it is to the vocal process of the arytenoid cartilage that the vocal ligament attaches. The cricoarytenoid joint allows movement classically described as rocking, gliding, and rotating, which results in the complex three-dimensional manipulation of the vocal folds [76, 77].

In addition to the arytenoid cartilages, the supraglottis is comprised of the epiglottis and two paired sesamoid cartilages, the cuneiform and corniculate. The epiglottis attaches to the internal and anterior midline surface of the thyroid cartilage and projects superiorly into the hypopharynx. The epiglottis is connected to the arytenoid cartilages by the aryepiglottic folds, which also house the cuneiform and corniculate cartilages. In the neonate, the arytenoids are often quite prominent on endoscopic view, and the epiglottis may appear highly curved, or omega shaped. Occasionally, this supraglottic tissue may become obstructive, leading to the clinical entity known as laryngomalacia. The prominence of the arytenoid cartilages diminishes by adulthood.

Aside from the bony-cartilaginous framework of the larynx, there are two fibroelastic structures which also contribute to the structure and function of the larynx. The first, known as the quadrangular membrane, attaches to the epiglottis anteriorly and then wraps around within the aryepiglottic folds to attach to the arytenoid cartilages. The quadrangular membrane also travels inferiorly along the medial wall of the pyriform sinus. The second fibroelastic structure known as the conus elasticus, helps to support the true vocal folds. Roughly conical in shape, it extends from the vocal ligament, anterior commissure and vocal process to the superior border of the cricoid cartilage inferiorly. In addition to providing structure to the larynx, these fibroelastic structures are also barriers for the spread of malignancy [78].

Musculature

The intrinsic musculature of the larynx is responsible for the control of the vocal folds by manipulating the arytenoid cartilages and laryngeal framework. Though vocal folds are generally thought of as opening and closing in a two-dimensional plane, over the past several years, research has elucidated much more complexity in vocal fold movement. In addition to opening and closing the glottic aperture, the laryngeal muscles also change the shape, volume, and tension of the vocal folds. Generally, the intrinsic muscles are described as adductors (lateral cricoarytenoid, thyroarytenoid, interarytenoid), abductors (posterior cricoarytenoid), and tensors (cricothyroid). The adductor muscles work to bring the vocal folds together in the midline. As the name implies, the lateral cricoarytenoid muscle originates on the lateral aspect of the cricoid cartilage and attaches to the muscular process of the arytenoid cartilage [29, 48,

72, 76, 77]. The paired thyroarytenoid muscles attach anteriorly to the inner surface of the thyroid cartilage and posteriorly to the bases of the arytenoid cartilages. Divided into two separate muscle compartments—the medial vocalis muscle and the lateral muscularis portion—the thyroarytenoid muscle is the bulk of the vocal folds and contributes to adduction. The sole unpaired laryngeal muscle, the interarytenoid, spans posteriorly between both arytenoid cartilages. In addition to being unpaired, it is also unique in that it receives bilateral innervation from the recurrent laryngeal nerve, and has been shown to contribute both to adduction and abduction of the vocal folds [79]. The primary vocal fold abductor is the posterior cricoarytenoid (PCA) muscle, which originates on the posterior cricoid cartilage and attaches to the muscular process of the arytenoid process. Recent work has shown that each PCA muscle is actually at least two distinct bellies with different histology and functions. However, broadly speaking, PCA contraction rotates the vocal process superiorly and laterally to open the glottis [80].

The only intrinsic laryngeal muscles that do not articulate on the arytenoid cartilages are the cricothyroid muscles which instead attach to the anterior surfaces of thyroid and cricoid cartilages. Cricothyroid contraction draws the two cartilages together anteriorly and tilts the cricoid cartilage posteriorly, which increases the distance between the anterior commissure and the vocal process of the arytenoid cartilage. The end result is a vocal fold elongation and increased tension [74]. This is also the only intrinsic laryngeal muscle which is not innervated by the recurrent laryngeal nerve.

Extrinsic laryngeal musculature includes the cervical strap muscles, the sternothyroid, sternohyoid, omohyoid, and thyrohyoid, as well as the mylohyoid, digastric, and stylohyoid muscle, which suspend the larynx from the skull base and mandible. This set of muscles primarily work to elevate and depress the larynx to assist with deglutition.

Innervation

The larynx is innervated by two branches of the vagus nerve—the superior laryngeal nerve and the recurrent laryngeal nerve. The intrinsic laryngeal musculature is innervated by the recurrent laryngeal nerve, named such because of its descent into the chest prior to looping back up into the neck. Because of its close association with the aorta and subclavian artery, vocal cord paralysis following cardiac surgery is a common occurrence in the pediatric population [81]. When assessing for paralysis on bronchoscopy, it is important that the anesthesiologist allow the child to maintain spontaneous respirations. Vocal fold movement should be symmetric, with abduction coordinated with inspiration. The best time to assess vocal fold motion, though, is during an awake exam as anesthesia can impair the interpretation of vocal fold motion.

As was previously mentioned, the only intrinsic laryngeal muscle that does not receive motor input from the recurrent laryngeal nerve is the cricothyroid muscle which instead is innervated by the external branch of the superior laryngeal nerve. The internal branch of the superior laryngeal nerve receives sensory stimuli from the larynx. The laryngeal mucosa is densely populated by mechanical, thermal, chemical, and taste receptors. As will be further discussed in the context of the physiology of the larynx, these sensory receptors play a role in the protective reflexes of the larynx as well as in the regulation of respiration.

Endoscopically Relevant Anatomy

A description of the topographic anatomy of the human larynx is an integral part of any endoscopic evaluation of the airway. It is helpful to do this in a sequential manner, in the order in which the structures and surfaces are encountered endoscopically. Here, it is important to understand the division of the larynx into three separate regions: the supraglottis, the glottis, and the subglottis. Depending on findings within the pharynx, a clear visualization of the laryngeal aperture—the area within the epiglottis, aryepiglottic folds, and interarytenoid space—may be challenging to obtain. Laryngomalacia, glossoptosis, vallecular cysts, vocal fold paralysis, or mass effect from extrinsic cervical pathology may distort laryngeal anatomy. Assessing for symmetry and ease of endoscopic exposure are critical initial components of the laryngeal evaluation.

Supraglottis

The supraglottis includes the epiglottis, the arytenoid cartilages, the false vocal folds, and the laryngeal surfaces of the aryepiglottic folds bilaterally. Special attention should be paid to the shape, size, and positioning of the epiglottis and arytenoid cartilages. In the neonate or premature child, it is not uncommon to see a highly curved epiglottis, often referred to as omega-shaped. The arytenoid cartilages may be especially prominent in the newborn larynx, prolapsing into the laryngeal airway with inspiration. The aryepiglottic folds may appear shortened, leading to a retroflexion of the epiglottis even during inspiration. At times, this constellation of features may lead to airway obstruction or feeding difficulties and is diagnosed as laryngomalacia.

Within the laryngeal aperture, the next structure to be examined should be the false vocal folds, which appear as symmetric mounded tissue immediately superior and lateral to the true vocal folds. These give way to the laryngeal ventricle—a mucosa-lined invagination that separates the true vocal folds from the false vocal folds. At the anterior extent of the ventricle bilaterally is the laryngeal saccule, a diverticulum lined with mucus and serous glands. Secretions from these glands help to lubricate the true vocal folds whose surface epithelium lacks mucus glands. The laryngeal saccule is not routinely examined endoscopically; however, rarely, it becomes dilated by air (laryngocele) or fluid (saccular cyst) and may appear as supraglottic asymmetry causing hoarseness, dysphagia, and airway obstruction [82, 83] (Fig. 3.8).

Glottis

The lateral aspect of the laryngeal ventricle marks the transition from supraglottis to glottis. Perhaps the most recognizable anatomic landmark of the endoscopically visualized larynx is the rima glottidis. The rima glottidis is the opening between the vocal folds and arytenoid cartilages extending from the anterior to posterior commissures. The anterior two-thirds of the vocal folds from the vocal processes to the anterior commissure are referred to as membranous glottis. The cartilaginous glottis lies posterior to the vocal processes. Viewed endoscopically, the vocal folds should appear symmetric and smooth with clean edges. Prominent vasculature, thickened mucus, irregular borders, lesions, and any asymmetry should be noted. More refined and specialized evaluation of vocal fold function and anatomy is best accomplished using videostroboscopy in the awake patient. However, gross motor function and the aforementioned qualities of the glottis should be remarked upon (Fig. 3.9).

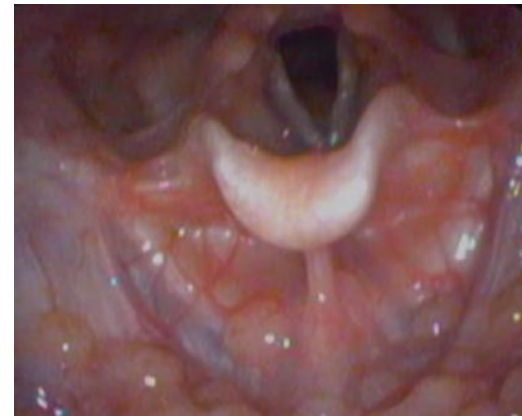

Fig. 3.8 Normal vallecular, supraglottis, and glottis. Notice the prominent median and lateral glossoepiglottic folds

Subglottis

Directly below the vocal folds, extending to the inferior edge of the cricoid cartilage is the subglottis. In the neonate, this is the narrowest segment of the airway and is a common site for airway pathology. The subglottis increases in size significantly during the first 3 years of life followed by a more linear pattern of growth until the adult larynx is reached [75]. Subglottic evaluation and pathology will be detailed extensively later in this volume.

Vocal Fold Histology

The membranous vocal fold, colloquially referred to as the vocal cord, spans the laryngeal opening from the inner surface of the thyroid cartilage at the anterior commissure to the vocal process of the arytenoid cartilage. Maculae flava at each attachment are responsible for the synthesis of the intervening vocal ligament. The area posterior to the vocal process is referred to as the cartilaginous glottis and does not play as significant a role in phonation.

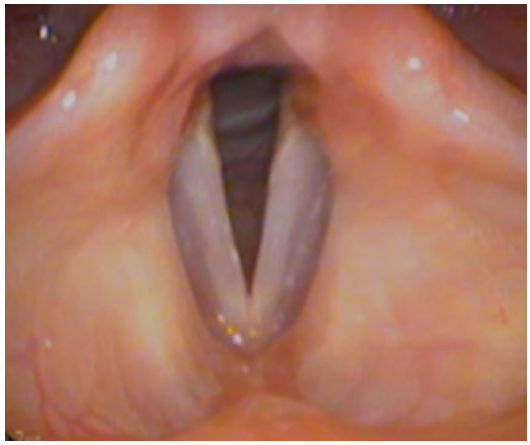

Fig. 3.9 Glottis, demonstrating true vocal folds, laryngeal ventricle, and false vocal folds

No discussion of the anatomy and physiology of the larynx would be complete without a description of the microstructure of the vocal fold. The vocal fold is a layered structure consisting of an epithelial surface layer, basement membrane, and a lamina propria, which is divided into three distinct layers over the vocalis muscle. While most of the larynx is covered with pseudostratified columnar respiratory epithelium, the vocal fold epithelium is stratified squamous. Immediately deep to the basement membrane of this epithelium is the superficial lamina propria, an acellular layer composed of extracellular matrix proteins and a few collagen and elastin fibers. This loose, gelatinous layer allows the overlying epithelium to vibrate freely and glide over the underlying muscle. The underlying intermediate and deep layers which together comprise what is referred to as the vocal ligament contain increasingly higher concentrations of collagen and elastin fibers. The deepest layer which is in contact with the underlying muscle is the most densely organized collagen fibers. The vocalis muscle, then, is immediately deep to the vocal ligament and makes up the bulk of the vocal fold. Anteriorly, the vocalis muscle attaches to the inner surface of the thyroid cartilage via a dense collection of connective tissue known as Broyles ligament. At this location, the inner perichondrium of the thyroid cartilage is absent [71, 72].

Whereas the neonatal larynx is primarily concerned with respiration there are several differences between the newborn and adult larynx which indicate the increasing importance of phonation and nuanced voice production with age. At birth, the vocal fold lacks any structure resembling the vocal ligament. The maculae flava are immature, but as the child develops, they begin to synthesize the collagen and elastin fibers that will contribute to the layered structure of the lamina propria [84–86]. Consequently, the newborn glottis does not have the layered structure required for mature phonation. Additionally, while the adult glottis is approximately 60–70% membranous, the neonate glottis is often closer to 30–40% membranous [75].

Physiology

Phonation

In addition to protecting the lower airway and helping to regulate respiration, the larynx has evolved in humans for phonation. The study of voice and phonation is a vast topic which is largely beyond the scope of this chapter. However, the basic concept behind voice production and the anatomy of the vocal fold and larynx will be reviewed here.

As discussed previously, the vocal fold is a layered structure consisting of an epithelial surface layer, basement membrane, and a lamina propria which is divided into three distinct layers over the vocalis muscle.

The myoelastic-aerodynamic theory of voice production was first introduced by Van den Berg and helps to described how subglottic air entrained over the vocal folds produces vibrations. The shape, size, and tension of the vocal folds are controlled by a complex interplay of neuromuscular control to produce vibrations. The passage of air from a high-pressure region (subglottis) to a low-pressure region (supraglottis) is controlled by muscular alterations in shape, size, and tension of the vocal folds to generate what is referred to as a mucosal wave due to the Bernoulli effect. This wave causes the inferior surface of the vocal folds to deflect medially to close. As the wave moves from inferior to superiorly, the surface is deflected first medially and then laterally, causing the folds to repeatedly

open and close [72, 87, 88]. Hirano's Body Cover theory explains the interplay between the muscular body of the vocal fold and the overlying lamina propria. Even while the vocalis muscle tightens and contracts, the overlying epithelium is able to freely move, deform, and vibrate [89]. This is only possible due to the previously described histologic make-up of the vocal fold.

Airway Protection

Perhaps the most critical function of the human larynx is to protect the lower airway from aspiration and inhalation of potentially harmful substances. Positioned at the distal end of the pharynx, and anterior to the esophagus, glottic closure is an integral part of the swallow mechanism, helping to safeguard from aspiration. Protective closure of the larynx in response to stimuli results in closure at three levels—at the level of the arytenoids and aryepiglottic folds, at the level of the false vocal folds, and finally at the level of the true vocal folds [90]. Accordingly, the surface of the larynx is populated by a large concentration of sensory receptors which respond to pressure, thermal, chemical, taste, and mechanical stimuli and participate in several protective reflexes [91, 92]. One such reflex that is especially salient during endoscopic evaluation of the larynx is that of laryngospasm, which can be triggered by various stimuli and causes the glottis to close forcefully—sometimes until long after the stimulus is removed [90, 93, 94]. Though protective in origin, laryngospasm has been hypothesized as the etiology behind Sudden Infant Death Syndrome (SIDS). Topical application of plain lidocaine over the larynx helps protect against laryngospasm during endoscopy.

Coughing, both reflexive and voluntary also demonstrates the larynx's role in airway protection. A cough helps to expel phlegm, mucus, or foreign material from airways and also helps to inflate the lower airways. The sequence of events that lead to a cough are a rapid and deep inhalation followed by glottis closure and initiation of expiration with resulting increase in intrathoracic pressure. The final stage in a cough involves opening the glottis rapidly, expelling air as quickly as 10 L/s [29, 95]. Both reflexive and voluntary cough share these three phases, though with voluntary cough, the amount and rate of inspired air have been shown to vary depending on strength of desired cough [95].

Respiratory Control

Finally, the larynx functions to control airflow. Acting as a valve, the glottis can control airflow and intrathoracic pressures by opening and closing. At the onset of inspiration, the posterior cricoarytenoid muscle fires to abduct the vocal folds prior to activation of the diaphragm. Similar rhythmic contraction of the cricothyroid muscle with respiration increases the anterior-posterior dimension of the larynx to facilitate inspiration [90, 96]. Again, the superior laryngeal nerve and its many sensory receptors on the laryngeal epithelium play a key role here.

Yet another example of the complex neuromuscular control of the larynx with respiration can be found in the laryngeal response to partial airway obstruction in the upper airway. The resulting decreased flow is detected by flow receptors of the superior laryngeal nerve. In response the posterior cricoarytenoid muscle contracts to open the glottis while the diaphragm simultaneously diminishes its inspiratory force. If not for these alterations, the negative pressure generated in the trachea and distal airways would result in airway collapse. [48] The laryngeal abductors again open widely and remain open longer during forceful expiration, whereas during panting, the abductors remain activated throughout.

References

1. Schwab JA, Zenkel M. Filtration of particulates in the human nose. Laryngoscope. 1998;108:120–4.
2. Ferris BG, Mead J, Opie LH. Partitioning of respiratory flow resistance in man. J Appl Physiol. 1964;19:653–8.
3. Sahin-Yilmaz A, Naclerio RM. Anatomy and physiology of the upper airway. Proc Am Thorac Soc. 2011;8:31–9.
4. Van Cauwenberge P, Sys L, De Belder T, Watelet J-B. Anatomy and physiology of the nose and the paranasal sinuses. Immunol Allergy Clin N Am. 2004;24:1–17.

5. Kridel R, Sturm-O'Brien A. Nasal septum. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Robbins KT, Thomas JR, Lesperance MM, editors. Cummings otolaryngology. 6th ed. Philadelphia: Elsevier/Saunders; 2015. p. 474–92.
6. Leung RM, Walsh WE, Kern RC. Sinonasal anatomy and physiology. In: Johnson JT, Rosen CA, editors. Bailey's head and neck surgery–otolaryngology. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2014. p. 359–70.
7. Hsu DW, Suh JD. Anatomy and physiology of nasal obstruction. Otolaryngol Clin N Am. 2018; https://doi.org/10.1016/j.otc.2018.05.001.
8. Neskey D, Eloy JA, Casiano RR. Nasal, septal, and turbinate anatomy and embryology. Otolaryngol Clin N Am. 2009;42(193–205):vii.
9. Flanagan P, Eccles R. Spontaneous changes of unilateral nasal airflow in man. A re-examination of the "nasal cycle". Acta Otolaryngol. 1997;117:590–5.
10. Hanif J, Jawad SSM, Eccles R. The nasal cycle in health and disease. Clin Otolaryngol. 2000;25:461–7.
11. Hasegawa M, Kern EB. The human nasal cycle. Mayo Clin Proc. 1977;52:28–34.
12. Courtiss EH, Gargan TJ, Courtiss GB. Nasal physiology. Ann Plast Surg. 1984;13:214–23.
13. Pevernagie DA, De Meyer MM, Claeys S. Sleep, breathing and the nose. Sleep Med Rev. 2005;9:437–51.
14. Proctor DF. Nasal mucous transport and our ambient air. Laryngoscope. 1983;93:58–62.
15. Baroody FM, Naclerio RM (2015) Allergy and immunology of the upper airway. Cummings Otolaryngology.
16. O'Neil JT, Mims JW (2014) Allergic rhinitis. Bailey's Head and Neck Surgery–Otolaryngolgy.
17. Cole P, Haight JS. Posture and the nasal cycle. Ann Otol Rhinol Laryngol. 1986;95:233–7.
18. Widdicombe JH. Regulation of the depth and composition of airway surface liquid. J Anat. 2002;201:313–8.
19. Boek WM, Graamans K, Natzijl H, van Rijk PP, Huizing EH. Nasal mucociliary transport: new evidence for a key role of ciliary beat frequency. Laryngoscope. 2002;112:570–3.
20. Goldstein NA, Tomaski SM. Embryology and anatomy of the mouth, pharynx, and esophagus. In: Bluestone CD, Simons JP, Healy GB, editors. Bluestone and Stoole's pediatric otolaryngology. 5th ed. Shelton Connecticut: People's Medical Publishing House; 2014. p. 1123–44.
21. Travers J. Physiology of the oral cavity.
22. Sreebny LM. Saliva in health and disease: an appraisal and update. Int Dent J. 2000;50:140–61.
23. Keesman M, Aarts H, Vermeent S, Häfner M, Papies EK. Consumption simulations induce salivation to food cues. PLoS One. 2016;11:e0165449.
24. Shaw SM, Martino R. The normal swallow: muscular and neurophysiological control. Otolaryngol Clin N Am. 2013;46:937–56.
25. Miller AJ. The neurobiology of swallowing and dysphagia. Dev Disabil Res Rev. 2008;14:77–86.
26. Lowe AA. Tongue movements–brainstem mechanisms and clinical postulates. Brain Behav Evol. 1984;25:128–37.
27. Sinacori J, Derkay CS. Physiology of the mouth, pharynx, and esophagus. In: Bluestone CD, Simons JP, Healy GB, editors. Bluestone and Stoole's pediatric otolaryngology. 5th ed. Shelton Connecticut: People's Medical Publishing House; 2014. p. 1151–60.
28. Fuller DD, Fregosi RF. Fatiguing contractions of tongue protrudor and retractor muscles: influence of systemic hypoxia. J Appl Physiol. 2000;88:2123–30.
29. Woodson G. Laryngeal and pharyngeal function.
30. Laitman JT, Reidenberg JS. The evolution and development of human swallowing: the most important function we least appreciate. Otolaryngol Clin N Am. 2013;46:923–35.
31. Moody MW, Chi DH, Mason JC, Phillips CD, Gross CW, Schlosser RJ. Tornwaldt's cyst: incidence and a case report. Ear Nose Throat J. 2007;86(45–7):52.
32. Miller RH, Sneed WF. Tornwaldt's bursa. Clin Otolaryngol Allied Sci. 1985;10:21–5.
33. Brandtzaeg P. Immunology of tonsils and adenoids: everything the ENT surgeon needs to know. Int J Pediatr Otorhinolaryngol. 2003;67(Suppl 1):S69–76.
34. Havas T, Lowinger D. Obstructive adenoid tissue: an indication for powered-shaver adenoidectomy. Arch Otolaryngol Head Neck Surg. 2002;128:789–91.
35. de Oliveira HF, Sampaio ALL, de Oliveira CACP, Teixeira MC, Miranda LA, Miranda DA. Evaluation of airway obstruction by adenoid tissue: comparison of measures in the sitting and recumbent. Int J Pediatr Otorhinolaryngol. 2012;76:1278–84.
36. Wang D, Clement P, Kaufman L, Derde MP. Fiberoptic examination of the nasal cavity and nasopharynx in children. Int J Pediatr Otorhinolaryngol. 1992;24:35–44.
37. Cassano P, Gelardi M, Cassano M, Fiorella ML, Fiorella R. Adenoid tissue rhinopharyngeal obstruction grading based on fiberendoscopic findings: a novel approach to therapeutic management. Int J Pediatr Otorhinolaryngol. 2003;67:1303–9.
38. Baldassari CM, Choi S. Assessing adenoid hypertrophy in children: X-ray or nasal endoscopy? Laryngoscope. 2013; https://doi.org/10.1002/lary.24366.
39. Parikh SR, Coronel M, Lee JJ, Brown SM. Validation of a new grading system for endoscopic examination of adenoid hypertrophy. Otolaryngol Head Neck Surg. 2006;135:684–7.
40. Perry M, Whyte A. Immunology of the tonsils. Immunol Today. 1998;19:414–21.
41. Jeyakumar A, Miller S, Mitchell RB. Adenotonsillar disease in children. In: Johnson JT, Rosen CA, editors. Bailey's head and neck surgery–otolaryngology. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2014. p. 1430–44.

42. Mathew OP, Abu-Osba YK, Thach BT. Influence of upper airway pressure changes on genioglossus muscle respiratory activity. J Appl Physiol. 1982;52:438–44.
43. Mathew OP, Abu-Osba YK, Thach BT. Influence of upper airway pressure changes on respiratory frequency. Respir Physiol. 1982;49:223–33.
44. Schweiger C, Manica D, Kuhl G. Glossoptosis. Semin Pediatr Surg. 2016;25:123–7.
45. Wilcox LJ, Bergeron M, Reghunathan S, Ishman SL. An updated review of pediatric drug-induced sleep endoscopy. Laryngoscope Investig Otolaryngol. 2017;2:423–31.
46. Lan M-C, Liu SYC, Lan M-Y, Modi R, Capasso R. Lateral pharyngeal wall collapse associated with hypoxemia in obstructive sleep apnea. Laryngoscope. 2015;125:2408–12.
47. Miller C, Purcell PL, Dahl JP, Johnson K, Horn DL, Chen ML, Chan DK, Parikh SR. Clinically small tonsils are typically not obstructive in children during drug-induced sleep endoscopy. Laryngoscope. 2016; https://doi.org/10.1002/lary.26447.
48. Woodson GE. Upper airway anatomy and function. In: Johnson JT, Rosen CA, editors. Bailey's head and neck surgery–otolaryngology. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2014. p. 868–78.
49. Marques M, Genta PR, Sands SA, Azarbazin A, de Melo C, Taranto-Montemurro L, White DP, Wellman A. Effect of sleeping position on upper airway patency in obstructive sleep apnea is determined by the pharyngeal structure causing collapse. Sleep. 2017; https://doi.org/10.1093/sleep/zsx005.
50. Strohl KP, Butler JP, Malhotra A. Mechanical properties of the upper airway. Compr Physiol. 2012;2:1853–72.
51. Trinder J, Woods M, Nicholas CL, Chan JKM, Jordan AS, Semmler JG. Motor unit activity in upper airway muscles genioglossus and tensor palatini. Respir Physiol Neurobiol. 2013;188:362–9.
52. Trinder J, Jordan AS, Nicholas CL. Discharge properties of upper airway motor units during wakefulness and sleep. Prog Brain Res. 2014;212:59–75.
53. Lo Y-L, Jordan AS, Malhotra A, Wellman A, Heinzer RA, Eikermann M, Schory K, Dover L, White DP. Influence of wakefulness on pharyngeal airway muscle activity. Thorax. 2007;62:799–805.
54. Certal VF, Zaghi S, Riaz M, Vieira AS, Pinheiro CT, Kushida C, Capasso R, Camacho M. Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2014; https://doi.org/10.1002/lary.25032.
55. Friedman M, Jacobowitz O, Hwang MS, Bergler W, Fietze I, Rombaux P, Mwenge GB, Yalamanchali S, Campana J, Maurer JT. Targeted hypoglossal nerve stimulation for the treatment of obstructive sleep apnea: six-month results. Laryngoscope. 2016;126:2618–23.
56. Lo Y-L, Jordan AS, Malhotra A, Wellman A, Heinzer RC, Schory K, Dover L, Fogel RB, White DP. Genioglossal muscle response to CO2 stimulation during NREM sleep. Sleep. 2006;29:470–7.
57. Brouillette RT, Manoukian JJ, Ducharme FM, Oudjhane K, Earle LG, Ladan S, Morielli A. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. J Pediatr. 2001;138:838–44.
58. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc. 2008;5:242–52.
59. Goldstein N. Evaluation and management of pediatric obstructive sleep apnea.
60. Miller MJ, Kiatchoosakun P. Relationship between respiratory control and feeding in the developing infant. Semin Neonatol. 2004;9:221–7.
61. Bautista TG, Sun Q-J, Pilowsky PM. The generation of pharyngeal phase of swallow and its coordination with breathing: interaction between the swallow and respiratory central pattern generators. Prog Brain Res. 2014;212:253–75.
62. Broussard DL, Altschuler SM. Central integration of swallow and airway-protective reflexes. Am J Med. 2000;108(Suppl 4a):62S–7S.
63. Miller AJ. Neurophysiological basis of swallowing. Dysphagia.
64. Matsuo K, Palmer JB. Coordination of mastication, swallowing and breathing. Jpn Dent Sci Rev. 2009;45:31–40.
65. Lefton-Greif MA. Pediatric dysphagia. Phys Med Rehabil Clin N Am. 2008;19:837–51, ix
66. Steele CM, Miller AJ. Sensory input pathways and mechanisms in swallowing: a review. Dysphagia. 2010;25:323–33.
67. Conklin JL, Christensen J. Neuromuscular control of the oropharynx and esophagus in health and disease. Annu Rev Med. 1994;45:13–22.
68. Vaiman M, Segal S, Eviatar E. Surface electromyographic studies of swallowing in normal children, age 4–12 years. Int J Pediatr Otorhinolaryngol. 2004;68:65–73.
69. Isaacson G. Developmental anatomy and physiology of the larynx, trachea, esophagus, and lungs. In: Bluestone CD, Simons JP, Healy GB, editors. Bluestone and Stoole's pediatric otolaryngology. 5th ed. Shelton, Connecticut: People's Medical Publishing House; 2014. p. 1397–406.
70. Sprinzl GM, Eckel HE, Sittel C, Pototschnig C, Koebke J. Morphometric measurements of the cartilaginous larynx: an anatomic correlate of laryngeal surgery. Head Neck. 1999;21:743–50.
71. Paulsen F, Kimpel M, Lockemann U, Tillmann B. Effects of ageing on the insertion zones of the human vocal fold. J Anat. 2000;196(Pt 1):41–54.
72. Noordzij JP, Ossoff RH. Anatomy and physiology of the larynx. Otolaryngol Clin N Am. 2006;39:1–10.
73. Jotz GP, Stefani MA, Pereira da Costa Filho O, Malysz T, Soster PR, Leão HZ. A morphometric study of the larynx. J Voice. 2014; https://doi.org/10.1016/j.jvoice.2014.03.008.

74. Storck C, Unteregger F. Cricothyroid joint type as predictor for vocal fold elongation in professional singers. Laryngoscope. 2017;128:1176–81.
75. Eckel HE, Koebke J, Sittel C, Sprinzl GM, Pototschnig C, Stennert E. Morphology of the human larynx during the first five years of life studied on whole organ serial sections. Ann Otol Rhinol Laryngol. 1999;108:232–8.
76. Kasperbauer JL. A biomechanical study of the human cricoarytenoid joint. Laryngoscope. 1998;108:1704–11.
77. Wang RC. Three-dimensional analysis of cricoarytenoid joint motion. Laryngoscope. 1998;108:1–17.
78. Mor N, Blitzer A. Functional anatomy and oncologic barriers of the larynx. Otolaryngol Clin N Am. 2015;48:533–45.
79. Hunter EJ, Titze IR, Alipour F. A three-dimensional model of vocal fold abduction/adduction. J Acoust Soc Am. 2004;115:1747–59.
80. Asanau A, Timoshenko AP, Prades J-M, Galusca B, Martin C, Féasson L. Posterior cricoarytenoid bellies: relationship between their function and histology. J Voice. 2011;25:e67–73.
81. Itagaki T, Kikura M, Sato S. Incidence and risk factors of postoperative vocal cord paralysis in 987 patients after cardiovascular surgery. Ann Thorac Surg. 2007;83:2147–52.
82. Civantos FJ, Holinger LD. Laryngoceles and saccular cysts in infants and children. Arch Otolaryngol Head Neck Surg. 1992;118:296–300.
83. Massoth LJ, Digoy GP. Flexible carbon dioxide laser-assisted endoscopic marsupialization and ablation of a laryngeal saccular cyst in a neonate. Ann Otol Rhinol Laryngol. 2014; https://doi.org/10.1177/0003489414525343.
84. Sato K, Hirano M, Nakashima T. Fine structure of the human newborn and infant vocal fold mucosae. Ann Otol Rhinol Laryngol. 2001;110:417–24.
85. Sato K, Hirano M. Histologic investigation of the macula flava of the human newborn vocal fold. Ann Otol Rhinol Laryngol. 1995;104:556–62.
86. Sato K, Hirano M. Histologic investigation of the macula flava of the human vocal fold. Ann Otol Rhinol Laryngol. 1995;104:138–43.
87. Jiang J, Lin E, Hanson DG. Vocal fold physiology. Otolaryngol Clin N Am. 2000;33:699–718.
88. Miri AK. Mechanical characterization of vocal fold tissue: a review study. J Voice. 2014;28:657–67.
89. Hirano M. Morphological structure of the vocal cord as a vibrator and its variations. Folia Phoniatr (Basel). 1974;26:89–94.
90. Sasaki CT, Buckwalter J. Laryngeal function. Am J Otolaryngol. 1984;5:281–91.
91. Widdicombe J, Lee LY. Airway reflexes, autonomic function, and cardiovascular responses. Environ Health Perspect. 2001;109(Suppl 4):579–84.
92. Widdicombe J. Airway receptors. Respir Physiol. 2001;125:3–15.
93. Suzuki T, Nakazawa K, Shiba K. Swallow-related inhibition in laryngeal motoneurons. Neurosci Res. 2010;67:327–33.
94. Bauman NM, Sandler AD, Schmidt C, Maher JW, Smith RJ. Reflex laryngospasm induced by stimulation of distal esophageal afferents. Laryngoscope. 1994;104:209–14.
95. Magni C, Chellini E, Lavorini F, Fontana GA, Widdicombe J. Voluntary and reflex cough: similarities and differences. Pulm Pharmacol Ther. 2011;24:308–11.
96. Bartlett D. Respiratory functions of the larynx. Physiol Rev. 1989;69:33–57.

Lower Airway Anatomy

4

Colin Wallis

Introduction

A detailed and intimate knowledge of the normal anatomy of the paediatric airway is essential for any bronchoscopist undertaking studies in children. There are important anatomical differences that occur with growth and normal variants need to be recognized.

In the previous section the upper airways (from the nasal entrance to the subglottic area) were described. Here we review the paediatric airway below the cricoid bone.

Familiarity of this anatomy comes from repeated examinations of the airway, preferably adopting the same "route" on each evaluation, and recognizing landmark configurations for orientation. The trachea and carina are the most obvious example. Return to these recognizable points when lost or confused. In this way, recognition of the normal anatomy becomes intuitive and with this comfortable familiarity comes the ready recognition of normal variants and pathological changes.

In this chapter's description of the lower airway anatomy, it is anticipated that the bronchoscopist is standing at the child's head and facing down the bronchial tree with the patient's right side on the right of the bronchoscopist. The lower airways are then traditionally divided into the extrathoracic trachea, the intrathoracic trachea and carina, the main right and left bronchi, the lobar bronchi and their subsequent divisions. A competent paediatric bronchoscopists should have a ready recognition of this normal anatomy down to these lobar subdivisions.

The Normal Trachea and Carina

The normal trachea is instantly recognizable by the anterior cartilaginous rings with an absent section posteriorly that is bridged by a softer pars membrana (membranous trachea) consisting of the trachealis muscle. In the newborn child and infant the rings can have a wider gap across their posterior section. With growth the rings adopt a more C-shaped appearance and in the older child the arc will extend to nearly 320 degrees. Adolescent females tend to preserve a round configuration, while males tend to have some sagittal widening and transverse narrowing.

The ends of the tracheal cartilage "rings" should not meet. Completely fused rings or nearly fused rings are not a normal variant.

The normal tracheal lumen is unobstructed and viewed bronchoscopically as straight without branches. Pulsation of the large vessels and right atrium which normally abut on the trachea and main bronchi may cause pulsatile deflections through the wall around the level of the

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_4

carina but the lumen should not obstruct or permanently distort in the normal subject. The airway should maintain its integrity during quiet breathing with some narrowing of the cross-sectional area due to inward bulging of the membranous trachea. With coughing, especially in the younger child, there can be significant inward bulging of the trachealis and sometimes some loss of integrity of the cartilaginous component. Arbitrarily, a loss of internal shape to approximately 50% is considered within the normal range. Abnormal malacia may be masked by rigid instrumentation, positive pressure ventilation or heavy sedation and anaesthesia.

The normal trachea has sparse secretions that are clear, light and frothy and are easily suctioned away. Careful observation of these bubbles can reveal movement of the bubbles toward the larynx, indicating normal ciliary functioning. The mucosa is smooth throughout. The trachea consists of between 18 and 22 rings and enlarges in length and width with somatic growth. Like the larynx, the trachea is situated higher in infants with the upper extrathoracic section at the level of the fourth cervical vertebra. In adults the upper level descends to C6–C7.

Contrary to the numerous variations of lobar or segmental bronchial subdivisions, abnormal bronchi arising from the trachea or main bronchi are rare. A true tracheal bronchus is any bronchus originating from the trachea, usually within 2–6 cm of the carina. The finding of a tracheal bronchus supplying, most commonly, the right upper lobe is a common association with distal complete rings or abnormal pulmonary artery slings and thus not considered a normal variant. When the entire right upper lobe bronchus is displaced onto the tracheal bronchus, it is also called a "pig bronchus" and has a reported frequency of 0.2%. A prevalence of 0.1–2% for a right tracheal bronchus and 0.3–1% for a left tracheal bronchus has been found in bronchographic and bronchoscopic studies.

The tracheal carina is a key landmark on the bronchoscopist's journey through the paediatric airway and should be instantly recognizable and a point of reference at times of disorientation. It is a keel-shaped structure with a characteristic cartilaginous ring arrangement. (Fig. 4.1a). The angle of the carina is more obtuse in infancy and early childhood. In the first two years of life the carina is situated on the right of the mid line and successively becomes more medial. The carina adopts a more acute angle in adolescence and adulthood. This blunted appearance of the main carina in paediatric bronchoscopy examinations is true of many of the other airway bifurcations.

The Bronchial Tree

The carina is a valuable anatomical landmark and the point of division into the left and right-sided bronchial tree. Subsequent branching of the primary bronchial tree is remarkably consistent in humans although normal variants do occur at the subsegmental level, especially in the lower lobes.

A full examination of the bronchial tree should be completed in all procedures if possible and should preferably follow a systematic route. A suggested examination is described next.

The right lung bronchial anatomy

(i) On reaching the carina, the aperture of the right main bronchus (RMB) comes into clear view on the right and the scope should naturally enter. In newborns the right main stem bronchus is four times shorter than the left; at three years of age it is one-third and in adolescents it is half the length of the left main bronchus.

(ii) Shortly after entering the RMB the bronchus intermedius will be visible (Fig. 4.1b) and a turn of the bronchoscope tip towards the right side will bring the right upper lobe (RUL) orifice into clarity with its trifurcation into an apical, posterior and anterior divisions. These orifices should be widely patent. If the tip of the scope has remained in the correct orientation, the corresponding lobes should be arranged as per the image in Fig. 4.1c.

(iii) Withdrawing the scope, you enter the right bronchus intermedius. Two orifices will be noted. They are the right middle lobe (RML) anteriorly, and the right lower lobe

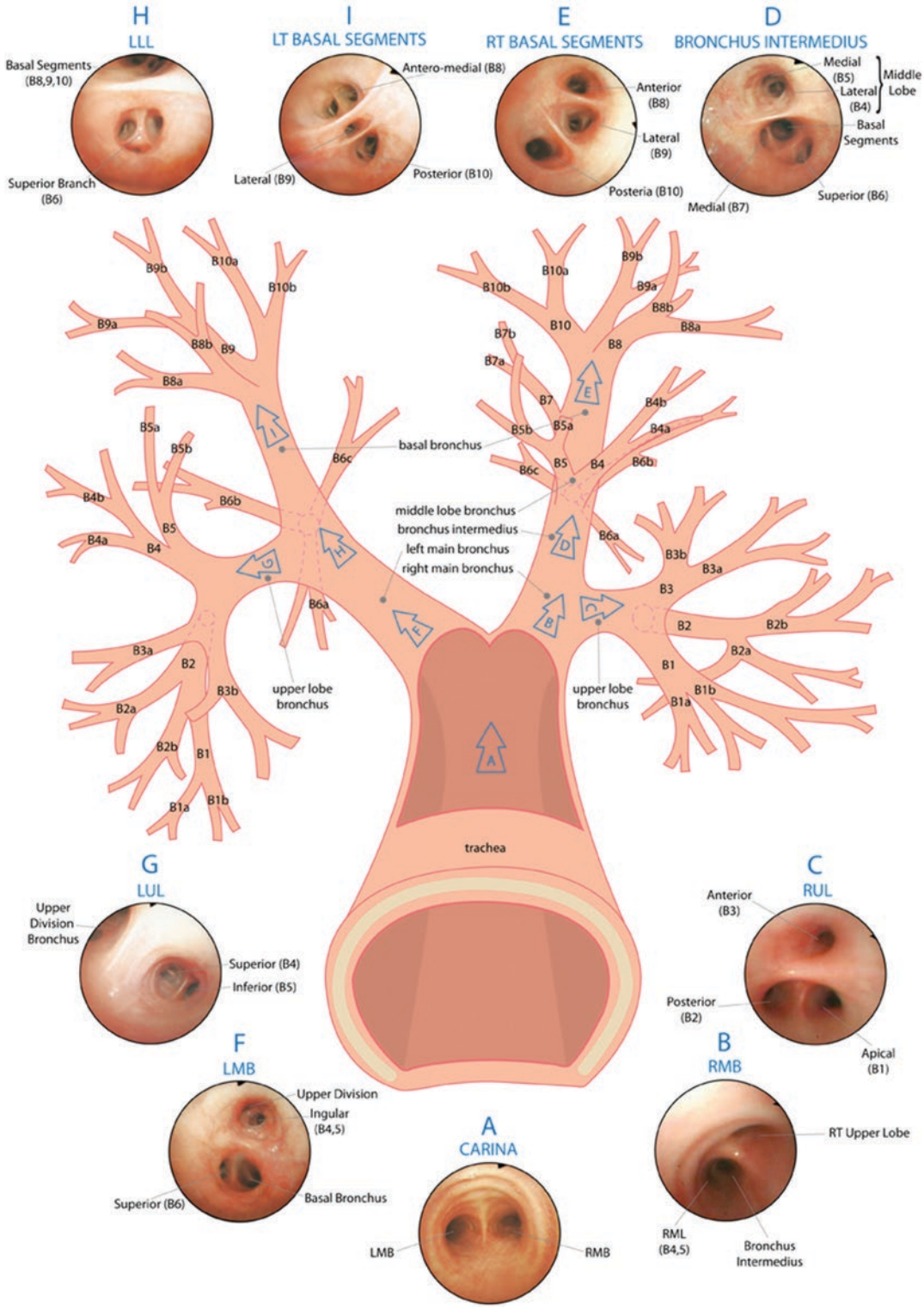


Fig. 4.1 The normal bronchial tree from the bronchoscopist's perspective. (Reproduced with permission from Wallis C. Paediatric Bronchoscopy. S. Karger AG, Basel 2010)

beneath the carinal division with observation of its early subdivisions (see v).

(iv) The RML is now entered to reveal its bifurcation into the medial and lateral segments each with their bifurcations.

(v) Withdraw the scope again and advance towards the RLL. The medial basal segment will branch off first along the medial side and the superior segment of the right lower lobe will appear on the opposite wall (Fig. 4.1d). Both these bronchi should be inspected at this stage.

(vi) At the distal end of the right bronchial tree you will see the anterior, lateral and posterior basal segments clustered together with a characteristic carinal pattern and known by this author as "the three musketeers" (Fig. 4.1e). Recognition of this cluster of bronchi is another useful anatomical landmark.

(vii) Return to the carina. If you did not evaluate the superior segment bronchus at step v, take the opportunity as you withdraw to do so now.

Left lung bronchial anatomy

(viii) From a position just above the carina, the opening of the left main bronchus (LMB) appears slightly smaller than the right and may not be seen "end on". The left main bronchus is longer than the right and, importantly, the upper division branching off to the left has a less acute angle (Fig. 4.1f) than you found for the RUL.

(ix) The upper division of the LUL commonly bifurcates into an apicoposterior and anterior segmental bronchus. Trifurcation at this point can be a normal variant.

(x) Withdraw the scope and enter the lingular segment of the LUL with its division into a superior and inferior branches. Practice will help distinguish the characteristic anatomy of the lingula segment from its neighbouring LUL (Fig. 4.1g).

(xi) Withdraw the scope and direct the tip towards the left lower lobe (LLL) bronchus. The superior segment of the LLL branches off postero-laterally and can be missed if proceeding too quickly (Fig. 4.1f). Distal to the opening of the superior segment, the three basal segments of the left lower lobe will be noted: the antero-medial, lateral, and posterior – in order and as illustrated in Fig. 4.1i. Individual bronchial openings for the antero-medial basal segment rather than a joint origin is a common normal variant.

(xii) Careful withdrawal of the bronchoscope back to the cricoid provides the opportunity to observe the dynamics of the airway if the patient is free breathing, and completes the inspection of the normal anatomy of the lower airways.

Normal Variants

There are a number of uncommon branching patterns that are considered normal variants. The principle of what constitutes a normal branching variant is that the bronchus should provide unobstructed airflow in inspiration and expiration to and from a normal lung structure distally and with congruous blood supply and free mucociliary clearance of secretions into the proximal airway. A normal variant will always be asymptomatic and discovered incidentally. Anatomical variations are most commonly seen in the left upper lobe and in the arrangements of the basal bronchi in the lower lobes. Examples are listed in Table 4.1.

One variant that may not necessarily be normal as per the definition above but is occasionally reported is the accessory cardiac bronchus. An accessory cardiac bronchus is a supernumerary bronchus from the inner wall of the right main bronchus or intermediate bronchus that progresses toward the pericardium (frequency 0.08%). Most accessory cardiac bronchi have a blind extremity, but imaging and anatomical studies have demonstrated that some develop into a series of small bronchioles, which may end in vestigial or rudimentary parenchymal tissue or even a ventilated lobule.

Table 4.1 Bronchial nomenclature

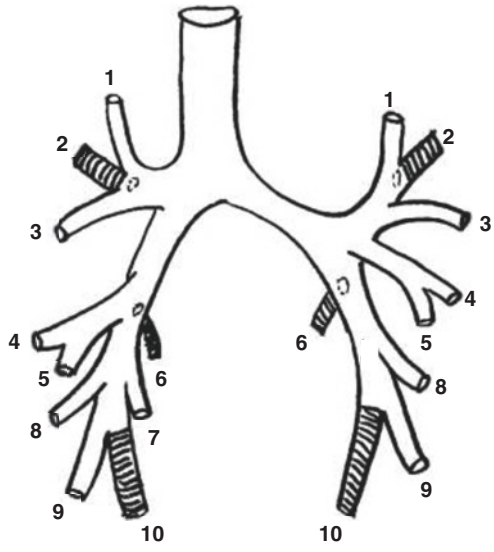
Anatomical nomenclature	Numbering system	Further subdivision	Common variations
Right upper lobe			
Apical	B^1	a and b	May be absent or arise from B2 or B3
Posterior	B^2	a and b	Numbering swapped around in Boyden system
Anterior	B^3	a and b	
Right middle lobe			
Lateral	B^4	a and b	May have a superior/inferior division similar to the lingula
Medial	B^5	a and b	
Right lower lobe			
Superior (apical)	B^6	a, b and c	
Medial basal	B^7	a and b	Occasionally there is an additional accessory cardiac branch
Anterior basal	B^8	a and b	The basal bronchi are the most variable divisions of the right lung
Lateral basal	B^9	a and b	
Posterior basal	B^{10}	a, b and c	
Left upper lobe			
Apicoposterior	B^{1+2}	a, b and c	May have a separate carina B^1, B^2
Anterior	B^3	a, b and c	
Superior lingular	B^4	a and b	
Inferior lingular	B^5	a and b	
Left lower lobe			
Superior (apical)	B^6	a, b and c	
Antero-medial basal	B^8	a and b	May have an additional medial bronchus B^7 with a separate anterior branch B^8
Lateral basal	B^9	a and b	
Posterior basal	B^{10}	a and b	May trifurcate into a, b, and c

Note: the Boyden surgical anatomical focus refers to the anterior and posterior segments of the upper lobe as B2 and B3. This nomenclature is not used by many bronchoscopists who prefer the Japanese system of Yamashita using anterior as B3 and posterior as B2

Bronchial Nomenclature

Standardisation of bronchial nomenclature has always been contentious. The lobar and segmental labelling used in this chapter, adopts the recommendations of a consensus meeting at a congress of anatomists in the 1950's. Inevitably it was not universally accepted and led to vigorous debate and correspondence. Although the descriptive terms I use above in describing the normal anatomy are widely used by paediatric bronchoscopists, alternative nomenclature still occurs. The term "apical" is often used interchangeably for the superior segment of the lower lobes. Similarly the term "dorsal" may be substituted for "posterior". Occasionally the lower lobe will be referenced as the inferior lobe.

In addition to the descriptive terms above, anatomists and radiologists have also devised a numbering system for the bronchial tree. This allows for detailed isolation of specific subdivisions beyond the primary nomenclature. Rather redundantly and perhaps confusingly, the letter B is used on each occasion. For example the apical segment of the upper lobe is labeled B1 and subsequent bifurcations are then given the label B1a and B1b with the facility for still further subdivision. Trifurcations, such as commonly occur in the antero-medial branch of the LLL or the posterior basal branches, are labeled a, b, and c. Clearly this has advantage in disciplines such as adult oncology, where there is a need for precise small tumour localisation in the lung. In practice, the majority of paediatric bronchoscopy procedures rarely need identifi-



RIGHT		LEFT	
1	Apical	1	apicoposterior
2	Posterior	2	
3	Anterior	3	Anterior
4	Lateral	4	Superior lingula
5	Medial	5	Inferior lingula
6	Superior	6	Superior
7	Medial basal	7	Generally absent
8	Anterior basal	8	Anterio-medial basal
9	Lateral basal	9	Lateral basal
10	Posterior basal	10	Posterior basal

Fig. 4.2 A schematic traditional diagram of bronchial anatomy indicating the numbering and nomenclature. The illustrated shaded bronchi travel in a posterior (dorsal) direction

cation beyond the anatomical descriptive nomenclature. For clarification, both systems are presented in Table 4.1 and in Fig. 4.2.

Bibliography

1. Ghaye B, Szapiro D, Fanchamps J-M, Dondelinger RF. Congenital bronchial abnormalities revisited. Radiographics. 2001;21:105–19.
2. Boyden EA, Clark SL, Danforth CH, Greulich WW, Corner GW. Science. 1942;96(2483):116.
3. Boyden EA. Segmental anatomy of the lungs. New York/Toronto/London: Graw-Hill; 1955.
4. Jackson CL, Huber JF. Correlated anatomy of the bronchial tree and lungs with a system of nomenclature. Dis Chest. 1943;9(4):319–26.
5. Jafek BW, Carter DR. Endoscopic nomenclature for bronchopulmonary anatomy. Otolaryngol Head Neck Surg. 1979;87(6):815–7.
6. Yamashita H. Roentgenologic anatomy of the lung 1st ed. 1978 Igaku-Shoin. Tokyo, Japan [Stuttgart, Germany]: Thieme; 1978.

Physiology of the Airways

5

Petr Pohunek

Introduction

The main role of the lungs is to supply oxygen for circulation and clear carbon dioxide from the blood. This is made possible by a complex alveolar system and pulmonary circulation. Before the gas exchange can occur, the air must be brought down to the alveoli from the ambient environment and after bidirectional gas transfer across the alveolar membrane, out of the lungs and away from the body. This conducting function is provided by the airways that do not participate in the gas transfer but whose primary function is to provide as much air as needed in any particular situation with as less effort and energy consumption as possible. The structure of the airways is adapted to this function and, under physiological situation, the airways are very effective in mediating the airflow to the alveoli. For a bronchoscopist, understanding the anatomy of the lungs and the airways is essential for orientation in the airways and interpretation of structural abnormalities in the bronchial tree. Understanding at least the basic physiological principles is critically important for safety of the procedure and for interpreting dynamic abnormalities within the airways. Breathing, be it spontaneous or artificially supported, always has some effect upon the airway lumen and needs to be always considered when preparing and performing the procedure and interpreting its results.

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Functional Aspects of the Airways

From the physiological point of view the airways are divided into upper and lower airways, the division between these two parts being the thoracic aperture. This division is based on the physiological fluctuation of intrathoracic pressure during the breathing cycle. From the trachea to the alveoli, the lower airways are a very complex system of branching airways with approximately 23 generations. The cross-sectional area of the branching airways increases from the trachea to the alveoli approximately 6000 times. Together with the airways there is also a similarly complex system of branching vessels originating from right heart circulation and the main pulmonary artery that eventually form the pulmonary capillary bed and guarantee the distribution of the exchanged gases into systemic circulation.

With inspiration, the activity of inspiratory muscles, mainly the diaphragm, distends the volume of the chest and thus generates negative intrathoracic pressure. Negative pressure of approximately −1 kPa below the atmospheric pressure is transferred via pleural space to the lung parenchyma, the lungs expand and the

S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_5

pressure in the intrathoracic airways drops. This leads to a pressure gradient between the atmosphere and the airways that generates inspiratory flow of the air (Fig. 5.1). The lower airways, exposed to the negative intrathoracic pressure, tend to dilate. The airflow in the upper (extrathoracic) airways is also associated with decrease of the intra-airway pressure even though there is no direct external negative pressure. The difference between the pressure in the upper airways and the external effect of the atmospheric pressure leads to some degree of compression and the upper airways tend to narrow with inspiration. During expiration, the passive elastic forces of the lung and the chest wall lead to decrease of the lung volume, driving the expiratory airflow. Passive expiration to the level of Functional Residual Capacity (FRC) usually does not cause significant change in the diameter of the airways as the intrathoracic pressure remains slightly negative, at the level of about −0.3 kPa. With active expiration, the intrathoracic pressure rises to positive values and its effect upon the airway wall may result in some degree of airway narrowing. This may be more expressed in preexisting airway narrowing (e.g., bronchoconstriction) or in structural defects of the airway wall, such as tracheo/bronchomalacia.

The forces that oppose extraluminal pressures and tend to keep airways open are the intraluminal pressure and the tethering forces of the lung parenchyma. As the intraluminal pressure decreases from the alveoli to the mouth, at certain point it equals the atmospheric pressure (Equal Pressure Point – EPP) (Fig. 5.2).

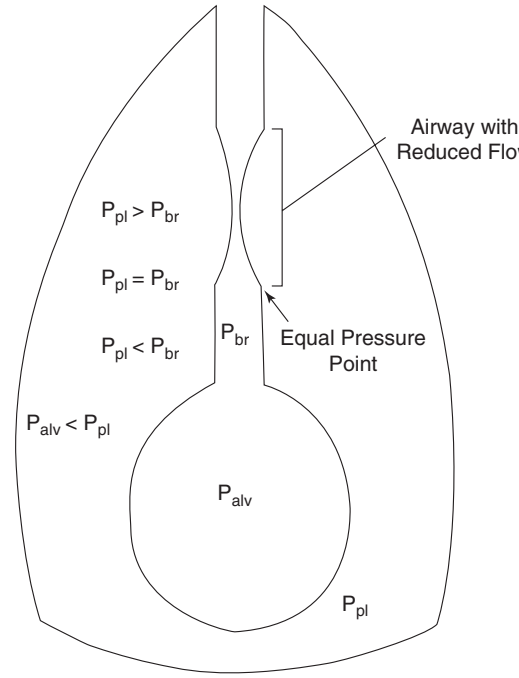

Fig. 5.2 Equal Pressure Point in relation to intrathoracic pressures

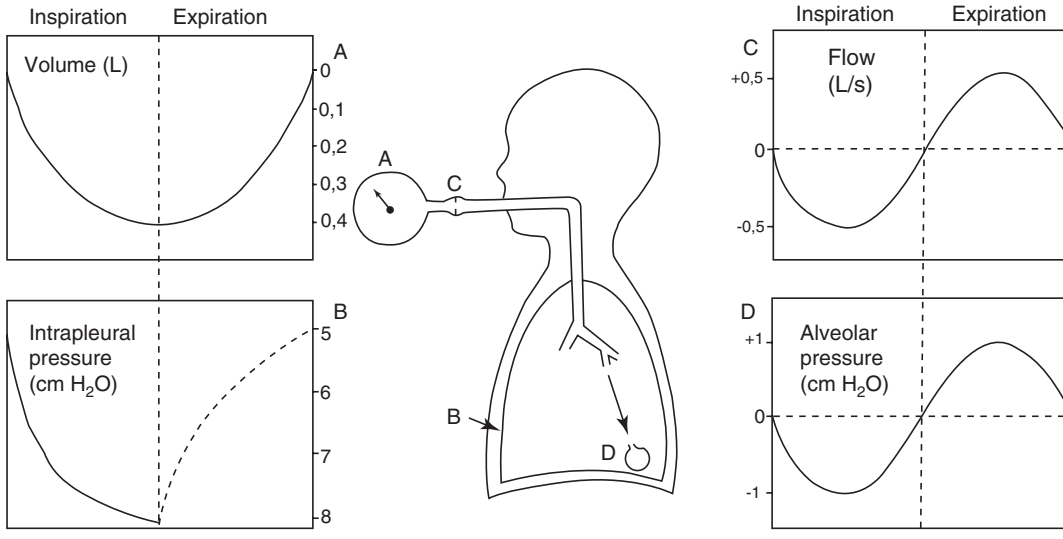

Fig. 5.1 Mechanics of breathing

The airways located orally from the EPP therefore tend to narrow and especially during active forced expiration the lumen can narrow significantly even despite the cartilaginous support. This may be more prominent during bronchoscopy procedures performed under conscious sedation with the patient breathing more forcefully. The location of the EPP varies and with airway obstruction it moves distally because of decreased intraluminal pressure. This can augment the obstruction even more, especially in more peripheral airways with less airway wall support. Breathing forces thus must be considered as possible confounding factors in interpreting airway patency and stability.

In the upper airways, the positive airway pressure leads to airway dilation and usually is not associated with any symptoms, unless there is a significant narrowing of the airway lumen that generates turbulent air flow and may lead to inspiratory or biphasic additional respiratory sound (stridor). Understanding the differences in pressure and flow effects in the upper and lower airways is important for interpretation of many respiratory symptoms. Appropriate description of additional respiratory sounds and timing of such symptoms in relation to the phases of respiratory cycle is critical for correct diagnosis.

Airway Patency and Resistance

Besides the driving pressures, the airflow in the airways is determined by airway resistance. Airway resistance is related to the structure and diameter of the airways and is influenced by airway anatomy together with some physiological factors, such as reflex tone of the airways. In addition, the airflow is also affected by some additional factors such as inhaled gas viscosity and type of airflow. Turbulent flow contributes significantly to the total airway resistance requiring higher pressures to maintain the same level of flow compared to laminar airflow. For laminar flow airway resistance is inversely related to the radius of the lumen to the power of 4 (Poiseuille's law).

$$R = \frac{8\mu l}{\pi r^4}$$

(R = resistance; l = length of the tube; r = radius; μ = gas viscosity)

From this equation it is apparent that the radius is the most important determinant of the resistance. This means that even a rather small decrease in airway patency leads to significant effect upon airway resistance. Decreasing the diameter of the airway by 50% would increase the resistance 16 times. With turbulent flow, resistance also increases due to the altered physical properties of the turbulent airflow.

Total airway resistance is composed by the sum of the resistance of the upper airways and resistance of the lower airways. Almost 50% is caused by the resistance of the nose, pharynx, and larynx and its level varies between nasal and oral breathing. The vocal cords partly open with inspiration, reducing resistance, and tend to partly adduct in expiration, forming some level of positive expiratory airway pressure. This may be significantly reversed in some pathological conditions, such as Inducible Laryngeal Obstruction (Vocal Cord Dysfunction).

Most of the resistance in the lower airways resides in the trachea, the main and segmental bronchi. Due to the physiological and physical changes occurring during the respiratory cycle, airway resistance is lower during inspiration and rises during expiration. It is not distributed equally in all parts of the respiratory tract. With any additional branching, the sum of airway resistance decreases even though the resistance of individual branches increases due to the reducing diameter. However, parallel arrangement of all the many individual resistances leads to lower total airway resistance. In adults, about 80% of the total airway resistance is determined by airways with more than 2 mm in diameter. Smaller airways determine less than 20% of the airway resistance as the sum of their lumens provide a large cross-sectional area. Even marked narrowing of the small peripheral airways (bronchioli) during some obstructive diseases does

not substantially change the total airway resistance.

In addition to the elastic recoil of the airway wall and the tethering forces of lung parenchyma, the central bronchi are supported by cartilage rings to protect against collapse. They can resist the external pressure much more than the more peripheral airways that lack similar support. However, as the rings are not complete, the membranous part of the bronchus may be pushed inwards by external pressure and limit patency of the lumen. Also, some events, such as edema, inflammation, or bronchoconstriction occur inside the cartilage rings and may lead to significant airway narrowing. Contraction of the bronchial smooth muscle is a result of increased bronchial responsiveness and is typically associated with bronchial asthma. However, in lesser extent it can occur also in individuals with no clinical signs of asthma in response to irritation of bronchial mucosa. This is mainly mediated by autonomic parasympathetic efferent nerves. Bronchoconstriction may be triggered by mediators (histamine, acetylcholine, bradykinin) but also by cold or osmotic changes. Hypoxia and hypercapnia also may initiate bronchoconstrictive reaction. Mechanical irritation during airway endoscopy is also a well-known trigger of airway narrowing, especially in subjects with highly reactive airways. On the other hand, deep inspiration may induce bronchodilation.

Standard lung function testing in co-operative children is mostly based on forced expiration (maximum flow-volume loop). The results of such examinations are influenced both by basic airway patency and collapsibility or compressibility of the airways. To differentiate between these two components, we may use the bronchodilation test with inhaled beta-2 agonist.

The Influence of Bronchoscopes upon Airway Function

The relation of the airway diameter and airway resistance must be well understood also when considering any additional airway narrowing, such as insertion of a bronchoscope. While rigid bronchoscope allows ventilation and may increase the resistance only to a certain level, insertion of a flexible bronchoscope may contribute to airway resistance significantly and even lead to compromised breathing. This should always be respected when preparing the procedure. The bronchoscope used should be of the smallest possible diameter to avoid unnecessary obstruction of airway lumen. This is even more critical in very young children and children with preexisting airway narrowing. To increase safety of the procedure, the child should be preoxygenated before bronchoscopy. However, it may still not be sufficient especially in neonates and young children whose lung volumes are low and their oxygenation reserve in apneic pause or largely decreased tidal volume may not be sufficient. In such children the procedure must be very short and usually consists of several short entries separated by enough time for appropriate recovery. In children with bronchial hyperresponsiveness, most guidelines suggest using pretreatment with inhaled beta-2 agonist to prevent bronchoconstriction and airway narrowing during the procedure. Reducing the airway lumen by inserting a bronchoscope can also increase pressure gradients and may increase collapsibility of the airways. This may lead to exaggerated interpretation of airway malacia or collapsibility. Another important issue is the use of suctioning during bronchoscopy. Excessive suctioning can interfere with the delivery of oxygen and may induce hypoxemia. Also, especially in very young children, it can lead to reduced parenchymal volume and induce atelectasis.

Mucociliary Clearance

An important physiological mechanism protecting the airways is the secretion of mucus and its transport out of the lungs together with some trapped small particles or bacteria. In healthy subjects the amount of mucus is minimal, and it is continuously transported together with the periciliary fluid by the ciliary epithelium in oral direction. During bronchoscopy this movement can be observed in real time as small bubbles on the air-

way surface moving in oral direction and crossing some landmarks, such as mucosal vessels or cartilage rings, at a speed of 6 to 20 mm per minute. In pathological conditions the amount of mucus can substantially increase, and mucus can change its properties. This, often together with impaired ciliary function, may result in significantly impaired clearance of mucus from the airways. Mucus secretion can be triggered by local irritation of mucosa during bronchoscopy. Together with edema and hyperemia it may be overinterpreted as chronic inflammation. Therefore, we should always judge the mucosa and the mucus secretion immediately after entering the airways before any secondary changes can occur.

Pulmonary Vessels

The three bronchial arteries supply systemic oxygenated blood to the bronchial tree and to some other structures, mainly nerves, vessels, and visceral pleura. They are connected to the pulmonary circulation, this provides oxygen also to the pulmonary parenchyma. Blood from this systemic circulation drains both through the pulmonary veins to the left atrium and via the bronchial veins to the right atrium. Bronchial arteries may react easily to chronic inflammation, increase their size and blood flow. They are the most common source of bleeding into the lungs, especially if the lung structure is damaged by chronic processes (e.g., bronchiectasis). In such situations interventional radiologist can embolize the bleeding artery; however, this should always be done with caution as after such intervention secondary ischemic changes can occur. On the other hand, often after successful closure of the bleeding vessel the collaterals develop rather quickly, and bleeding can recur.

The pulmonary artery receives the full cardiac output from the right ventricle and eventually distributes blood to the alveolar capillaries where the gas exchange occurs. This vascular system consists of conventional vessels accompanying the bronchial tree and, in addition, of supernumerary vessels that directly go to the alveolar units. Pulmonary veins bring the oxygenated blood to the left atrium also via conventional and supernumerary branches.

The pulmonary vascular bed forms a large surface area of approximately 70 to 80 sq. meters. Looking at the composition of the wall, pulmonary arteries can be differentiated according to the presence of smooth muscle and elastic fibers. This composition changes with the branching and size of the arteries and is also dependent on age.

Innervation of the Airways

The autonomic innervation of the airways and lung parenchyma originate from the parasympathetic vagus nerve and sympathetic upper thoracic ganglia. These nerves form the pulmonary plexus around the hilus and from there the neural fibers follow the airways and the vessels that obtain autonomic innervation from them. One of the basic functions of these nerves is to regulate airway tone with parasympathicus causing bronchoconstriction and adrenergic sympathicus causing bronchodilation. A similar effect could be expected also upon the vessels; however, this is not so expressed as in the bronchi. Under normal conditions the vessels are dilated and there is not so much variation of the vascular tone as it is the case with the airways.

The vagus nerve is also the origin of the sensory nerves that arise from slowly and rapidly adapting receptors and from C-fiber receptors. The slowly adapting stretch receptors are located in the airway smooth muscle and react to changes in transpulmonary pressure and increase in lung volume. Their stimulation results in bronchodilation, decrease in systemic blood pressure, increased heart rate, and, in young children, triggering the Hering-Breuer reflex of inspiratory inhibition.

The rapidly adapting receptors react to irritation of the airways or airway parenchyma and their stimulation leads to coughing, increased breathing activity, and constriction of the larynx and the bronchial wall.

C-fiber receptors are the terminal part of nonmyelinated vagal afferent branches and react to

pulmonary edema and congestion. They induce a sensation of dyspnea and shallow breathing and raise the pressure in the airways by expiratory laryngeal constriction.

Besides the two autonomic systems, there is another system labeled non-adrenergic, non-cholinergic system, whose function is mainly mediated by several neurotransmitters, such as substance P or vasoactive intestinal peptide (VIP). Its function has not been fully elucidated so far.

Lymphatic System

The lungs possess a broad network of lymphatic vessels that accompany blood vessels and take care of draining fluid that has left the circulation into the interstitial compartment. Draining the fluid back to the circulation helps to maintain appropriate fluid balance in the lung and prevent edema. Larger lymphatics are equipped with smooth muscle fibers in their wall whose contraction supports fluid transportation. The centripetal transport of lymph is supported by a system of monocuspid valves that prevent reverse flow. The lymphatic system also plays a role in pulmonary defense mechanisms. In relation to bronchoscopy, the location of lymph nodes is mainly important. Enlarged lymph nodes may compress the airways and also may be an important source of diagnostic material (using transbronchial needle aspiration).

Acknowledgment The author thanks Petra Dvořáková, M.D. (2nd Faculty of Medicine, Charles University, Prague, Czech Republic) for drawing the figures for this chapter.

Further Reading

1. Barret KE, Barman SM, Juan J, Brooks HL. Ganong's review of medical physiology. 26th ed: McGraw-Hill Education/Medical; 2019. p. 752.
2. Bates JHT. Systems Physiology of the Airways in Health and Obstructive Pulmonary Disease. Wiley Interdiscip Rev Syst Biol Med. 2016;8(5):423–37.
3. Brusasco V, Physiology A. In: Aliverti A, Brusasco V, Macklem PT, Pedotti A, editors. Mechanics of breathing. Milano: Springer; 2002.
4. Paleček F, et al. Patofyziologie dýchání [Pathophysiology of breathing]. Prague: Academia; 1987. p. 311.
5. Wilmott RW, Bush A, Deterding RR, Ratjen F, et al. Kendig's disorders of the respiratory tract in children. 9th ed: Elsevier; 2018.

6 Indications and Risks of Flexible Bronchoscopy in Children

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Indications

General Considerations

Flexible bronchoscopy in children is generally well tolerated and should be considered as a tool anytime it is the safest, easiest, and most effective way to obtain information and to intervene in the airway of the child [1]. Advantages that the flexible instrument has over the rigid bronchoscope include the ability to evaluate the entire upper and lower airway without artificial airway manipulation and to do so while the child is under light anesthesia. Also, only a flexible instrument is able to be passed through an endotracheal tube. Flexible bronchoscopes come in sizes appropriate for neonates to adults and can be used safely in a variety of settings. These scopes can be used in an outpatient setting with light sedation and can be used at bedside for an inpatient, making flexible bronchoscopy a useful tool in the neonatal and pediatric intensive care units [2–4]. With its utility, there are many indications for pediatric flexible bronchoscopy. Generally, there are two broad categories of indications for the procedure discussed here, diagnostic and therapeutic [5, 6].

Diagnostic Indications

A diagnostic indication is one in which flexible bronchoscopy is done to discern an etiology of a respiratory problem. Diagnostic indications commonly include chronic or recurrent symptoms, such as chronic cough, or chronic or recurrent diagnoses, such as recurrent pneumonia. Also in the category of diagnostic indications is the need for an airway evaluation. In this last category, a symptom may or may not be present; the bronchoscopy may be done only to see the airway such as in the case of a child that is ready to be extubated or have a tracheostomy tube removed. The general need to obtain a specimen, such as bronchoalveolar lavage fluid (BALF), might also be considered an indication, even without symptoms.

Chronic/Recurrent Symptoms

Children commonly have respiratory symptoms such as cough. The indication for bronchoscopy occurs when the symptom is chronic or recurrent and problematic. This usually means that medical treatment for remediation has been tried and failed prior to the bronchoscopy. Common

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_6

Table 6.1 Common Symptom Indications

Cough
Wheeze
Stridor
Hoarseness
Epistaxis
Hemoptysis
Cyanosis

symptoms leading to flexible bronchoscopy are listed in Table 6.1 [7].

Chronic cough is one of the most common indications for bronchoscopy in children. The most common causes of chronic cough are asthma, gastroesophageal reflux disease, and postnasal drip [8]. Treatment of presumed causes should occur first; and bronchoscopy should be performed if symptoms are unremitting or if other worrisome factors are present, such as hemoptysis, localized wheezing, or immunocompromised patient.

Wheeze is also a common indication for bronchoscopy. Wheeze is found in asthma, but if the wheeze is unresponsive to bronchodilator or anti-inflammatory medications or if the wheeze is localized, evaluation by bronchoscopy is indicated. Issues such as foreign body, tracheobronchomalacia, and intrinsic or extrinsic airway narrowing may be the cause and are best found on direct visualization [9–11].

Stridor in infants is often benign and due to laryngomalacia if ongoing or due to infectious croup if acute and self-limited. Stridor causing cyanosis or respiratory distress not relieved by acute treatment should be evaluated, as other lesions such as epiglottitis, papillomatosis, laryngeal-esophageal clefts, growing hemangioma, vascular compression, or foreign body could also be causal and are best diagnosed with flexible bronchoscopy [12–15]. Here the flexible bronchoscope has the advantage of being used without airway manipulation in a spontaneously breathing child to see from where the noise originates.

Hoarseness often presents to otolaryngologists instead of pulmonologists but should be evaluated if persistent. Congenital or acquired vocal cord paralysis or paresis and vocal cord nodules or papilloma may be causative [16]. Vocal cord dysfunction may lead to further evaluation such as a swallowing study to rule out aspiration or a brain MRI to rule out brainstem compression.

Hemoptysis in children is not as common as it is in adults but can be a significant problem. Blood from the airway may range from sputum streaked with blood in the case of bronchitis to massive hemoptysis from bronchovascular fistula. Bronchoscopy can help isolate hemoptysis from hematemesis or epistaxis, can help localize the bleeding site, or can help therapeutically manage the bleeding with the application of epinephrine, thrombin solutions, or use of a ballooned catheter [17–19].

Cyanosis alone may not be a common indication for flexible bronchoscopy, but its presence is concerning for worrisome pulmonary problems. A source should be found if a child is chronically hypoxic.

When a symptom leads to a flexible bronchoscopy, the procedure is able to evaluate the anatomy for lesions causing the symptom and also allow the bronchoalveolar lavage to potentially identify a specific etiology such as a specific infection. An example is a child who has had a chronic cough, has tried asthma therapy (bronchodilators and inhaled or systemic steroids), and persists in symptoms. Bronchoscopy evaluates the airway to find anatomical causes such as airway compression or malacia, airway inflammation or intrinsic airway narrowing and the bronchoalveolar lavage will then diagnose any infection or cellular inflammation.

Chronic/Recurrent Diagnoses

Children commonly have respiratory diagnoses. All children experience upper airway infections, often recurrent upper airway infections that do not require bronchoscopy. Flexible bronchoscopy is used when there is a chronic or recurrent process that is causing distress or harm to the child. The same as when a flexible bronchoscopy is done for a symptom, when it is done for a problem, structural airway abnormalities are visualized, and samples are obtained to find an etiology. Common diagnoses that lead to bronchoscopy are listed in Table 6.2 [7].

Croup is a common diagnosis in young children with viral infections. Treatment is based on

Table 6.2 Common diagnoses indications

Croup
Pneumonia
Atelectasis
Aspiration
Pulmonary Infiltrates
Bronchiectasis
Uncontrolled Asthma

severity of symptoms and the symptoms are generally self-limited. Recurrent croup, especially in an older child, may deserve bronchoscopy to evaluate for an anatomical issue leading to the symptoms. Children with subglottic stenosis or vocal cord issues will be more prone to croup. A child who wakes suddenly in the middle of the night without specific infectious triggers might have spasmodic croup triggered by gastroesophageal reflux. A bronchoscopy in this later case might diagnose upper airway and/or laryngeal inflammation along with evidence of aspiration of lipid on bronchoalveolar lavage.

Previous surveys of indications for bronchoscopy in children show that *pneumonia* or *recurrent pneumonia* is the most common indication [20]. The diagnostic yield of bronchoscopy for pneumonia depends on the circumstances. If a child is too young to expectorate sputum, a BAL is a nice alternative to obtain a specimen for microbiology. If a child is immunosuppressed (e.g., cancer or HIV), bronchoscopy with BAL is useful to find opportunistic infections such as fungal pathogens or pneumocystis. All bronchoscopy for active infection is best done if the child is off of antibiotics, as antibiotics may suppress the growth of organisms. In the case of recurrent pneumonia, bronchoscopy is useful to determine if airway abnormalities, foreign bodies or microaspiration could be causative [21, 22].

Atelectasis is a radiographic abnormality that may warrant bronchoscopy. Common etiologies are mucus plugging, foreign body, or airway obstruction from intrinsic (airway wall edema) or extrinsic (vascular compression) causes [23]. While this problem may also lead to a therapeutic bronchoscopy, often the main indication for the bronchoscopy is diagnostic to find the etiology of the atelectasis.

Pulmonary infiltrates are another radiologic indication for bronchoscopy. These may be synonymous with pneumonia, but may be more diffuse, fleeting or recurrent. Here, in addition to performing a BAL for culture, a BAL and airway evaluation may diagnose other reasons to have alveolar disease, such as microaspiration.

Bronchiectasis on chest radiograph or chest CT scan indicates airway damage and understanding why this has occurred may be a bronchoscopic indication. Bronchiectasis in children occurs with underlying diseased such as cystic fibrosis, primary ciliary dyskinesia, or immunodeficiency and can also occur after a single severe inflammatory event such as a bad pneumonia or foreign body aspiration. Additionally, bronchiectasis occurs with chronic aspiration of stomach contents, swallowing aspiration, or aspiration of saliva. The bronchoscopy and BAL is able to help determine the underlying and acute causes by visualizing the airway and by obtaining BALF for culture and cytology.

Uncontrolled asthma may be an indication for bronchoscopy if there is a suspicion that something else is contributing, such as indolent infection or aspiration of GER. Bronchoscopy here allows the visualization of the airway for inflammation and gets a BALF to understand the cellular inflammation and other potential contributors [24].

Remember that even if the indication is a respiratory problem, the main reason for the bronchoscopy may simply be to get BALF to guide therapy. Young children often do not spontaneously produce sputum and getting induced sputum requires a cooperative patient. BALF may be desired for culture, to look for aspiration or simply to follow up on a previously abnormal BALF. While the indication is a respiratory problem and these are diagnostic procedures, bronchoscopy is almost always done in order to guide a therapeutic change.

Airway Evaluation

This set of indications result from either a known or a suspected airway abnormality. Flexible bronchoscopy evaluates the airway from the nares to the bronchi, both upper and lower airway

issues. While airway evaluation might be undertaken primarily due to suspicion of a single site problem, a full airway evaluation should be done in almost every flexible bronchoscopic procedure. It might be a symptom or a diagnosis or a radiographic study that leads to the suspicion of an airway issue. Once an airway abnormality is known, the flexible bronchoscopy indication is to reevaluate the problem. Bronchoscopy guides the decision for intervention (e.g., surgery, decannulation) or for further evaluation (e.g., CT scan or videofluoroscopic evaluation of swallowing) [25]. It also can be a follow-up to evaluate the success of an intervention. Upper airway problems that may be seen on flexible bronchoscopy are listed in Table 6.3.

Careful evaluation of the upper airway should be part of any routine flexible bronchoscopy [26]. Starting at the nares in a child under light general anesthesia who is spontaneously breathing is best to evaluate the upper airway [11]. Evaluating for inflammation, mucus, obstruction, and other upper airway problems is part of a routine upper airway endoscopy and will aid in diagnosis of overall respiratory issues [27].

The lower airway also should be fully evaluated as well with light anesthesia. A symptom such as wheeze may indicate a lower airway abnormality. Lower airway problems that may be seen on flexible bronchoscopy are listed in Table 6.4.

As with upper airway abnormalities, these lesions may be suspected or known, and bronchoscopy may be used for initial discovery or following up a previous issue. While radiographic studies may give an indication of lower airway pathology, direct vision of the airway under light anesthesia is generally much better. Tracheobronchomalacia, for example, may be implied on CT scan or fluoroscopy, but in controlled studies the sensitivity of flexible bronchoscopy is significantly better [28, 29].

A small subset of bronchoscopic procedures for airway evaluation are done specifically because a child is unable to be extubated. The clinical team may not know what the issue is and may request a procedure to evaluate the airway for lesions that are preventing that extubation. Along these same lines, a common anatomical evaluation is done in preparation for decannulation or if a child is failing the common steps towards decannulation. If a child with a tracheostomy cannot tolerate capping, for instance, a bronchoscopy is able to help determine why and then guide subsequent interventions for the lesion [25]. In conjunction with surgeons, a flexible bronchoscopic evaluation can determine the success of a surgical intervention. Examples include airway visualization after tracheoesophageal fistula repair or after airway reconstruction for subglottic stenosis [30].

Diagnostic Bronchoalveolar Lavage

Part of the flexible bronchoscopy procedure is performing a bronchoalveolar lavage (BAL). This is done as an adjunct to most diagnostic procedures, but it is also done as the primary reason for the bronchoscopy. An example is a child with cystic fibrosis who has decreased lung function and needs to be treated with antibiotics but is unable to cough up adequate sputum for a culture. If there is concern that the epiglottic culture does not reflect the lower airway, BALF can be sent for bacterial, viral, fungal, and atypical pathogens.

Table 6.3 Upper airway findings/indications

Choanal atresia	Laryngomalacia
Adenotonsillar hypertrophy	Laryngeal stenosis/web
Sinus/nasopharyngeal drainage	Vocal cord paralysis/paresis/nodule
Nasal polyps/obstruction	Laryngoesophageal cleft
Pharyngeal collapse	Glottic stenosis
Glossoptosis	Subglottic stenosis

Table 6.4 Lower airway findings/indications

Tracheal stenosis	Bronchomalacia
Complete tracheal rings	Bronchial stenosis
Stoma issues (granulation/collapse)	Bronchial compression (Vascular/Tumor)
Tracheomalacia	Granulation tissue
Tracheal compression (Vascular/Tumor)	Hemangioma
Tracheoesophageal fistula or pouch	Foreign body

This same indication is true for other children in whom BALF culture is desired but they are unable to produce adequate sputum. These include children with primary ciliary dyskinesia, children with immunodeficiency and a fever, and even children where tuberculosis is suspected and a culture is needed. A final indication of BAL as a primary reason for a bronchoscopy would be a child who has been determined to be brain dead and needs BALF collected to determine if the lungs might be used in organ donation [1].

Endobronchial Biopsy

Here forceps or brush is introduced through the bronchoscope to obtain a cellular sample. Tissue can be a useful adjunct to diagnosing granulomatous disorders and tuberculosis. It can also be used to obtain ciliated epithelial cells for the diagnosis of primary ciliary dyskinesia [31]. Multiple research studies have utilized bronchial biopsies in inflammatory diseases such as asthma and cystic fibrosis to better understand the underlying immunologic processes [31–35].

Transbronchial Biopsy (TBB)

This is a procedure done commonly in adult flexible bronchoscopy in order to obtain peripheral airway cells for diagnosis and culture. The utility of this procedure to identify and stage acute rejection in lung transplant patients has been well established. Diagnosing infection in these same individuals is also readily possible [36]. TBB is also used to diagnose chronic rejection, bronchiolitis obliterans, and interstitial lung disease. The diagnostic yield in these latter conditions is not as good but still possible [37, 38]. TBB is difficult to perform in infants and young children, limited by the size of the bronchoscope necessary to introduce biopsy forceps into the small airways [39]. TBB is done with fluoroscopic guidance to place the biopsy forceps where expected and needed.

Transbronchial Needle Aspiration (TBNA) with Endobronchial Ultrasound (EBUS)

The procedure is used frequently in adult patients for the diagnosis of cancer. In children, the main utility is for the diagnosis of tuberculosis from airway lymph nodes and evaluation of peripheral pulmonary nodules with fluoroscopic guidance. The procedure is limited by the size of bronchoscope needed, currently a 4.0 mm bronchoscope with a 2.0 mm channel for radial EBUS, and by the size of the airway. For very small children, a biopsy might be limited to the main carina. Utility is not very well established, and this technique is only useful for individuals specially trained in this technique [40].

Therapeutic Indications

The second large category of indications is therapeutic. Here a flexible bronchoscopy is undertaken in order to have a therapeutic effect on the child. Often these indications occur in children who are hospitalized, in the intensive care unit, or intubated. Here a flexible bronchoscopy may often be safely performed at the bedside to achieve the desired effect [2]. Remember that many of these techniques may be utilized at once to achieve therapy and that techniques that seem to be best achieved with the rigid bronchoscope can often be aided by the flexible bronchoscope [6].

The first therapeutic indication is unremitting *atelectasis*. In a child who has persistent atelectasis on a chest film, a bronchoscopy can be done to remove any airway obstruction. The airway obstruction is commonly due to mucus plugging that can be suctioned away. Use of a flexible bronchoscope allows suction to be applied but also allows mucolytic medications to be applied directly to the plug [1]. Other tools to remove a large thick plug may include biopsy forceps or cryoprobe. Variations on mucus plugging include airway obstruction with blood clots or the extreme of obstruction with *plastic bronchitis*. This last category occurs in individuals with cardiac defects and sickle cell disease. Plastic bronchitis causes airway filling with thick casts (heavily lymphocytic) that require extensive suctioning, usually with the aid of medications or other instruments to remove the plugs. The use of tissue plasminogen activator directly on the plugs of plastic bronchitis has been effective [41].

Another therapeutic application is use of *whole lung lavage* for individuals with alveolar proteinosis or other alveolar filling process [39]. These patients have a collection of proteinaceous material in their alveoli from a surfactant processing error. The alveoli fill with material over several months and serial whole lung lavage is done to remove the material. One lung at a time is filled with repeated aliquots of warmed saline and then drained. This is done until the drained fluid clears. The second lung is done on a separate day. This is repeated whenever the lung symptoms become difficult. Eventually many children go into remission.

Aid to Intubation is a procedure often useful with a flexible bronchoscope, especially in a difficult airway, like that in a child with craniofacial abnormalities [39, 42]. This is one of the most common indications for flexible bronchoscopy in the critical care arena [2]. An ETT is slipped over the bronchoscope and inserted into the airway over the scope once the bronchoscope is in position in the lower airway. Most intubations occur via a nare, but this technique can also be used orally with the aid of a laryngeal mask or blade tongue retraction. An ETT as small as 2.5 mm may be inserted with the help of a 2.2 mm bronchoscope.

Foreign body removal is a somewhat controversial use of the flexible bronchoscope. There are multiple reports in the literature of foreign bodies being successfully retrieved by flexible bronchoscopes [43–50], but glottic and large foreign bodies may become dislodged more easily from the flexible bronchoscope and lead to frank airway obstruction. These foreign bodies should be removed by the rigid instrument. If a secure airway is in place and the foreign body is in a position to be easily removed by the flexible bronchoscope, this technique may be safely used. A rigid bronchoscope should, however, be available if necessary [39]. More distal, difficult to visualize with the rigid scope, objects may be best initially manipulated by the flexible bronchoscope. A flexible bronchoscope may always be used to visualize the airway and confirm the presence and location of a foreign body and may be used to help clean up the airway after foreign body removal.

Occasionally mass lesions will obstruct or partially obstruct the airway of a child. Granulomas, hemangiomas and bronchial carcinoid tumors are examples. When the lesion is an acquired lesion such as granulation tissue from deep suctioning in a patient with a tracheostomy tube, use of the *KTP laser* through a flexible bronchoscope can be helpful. The KTP laser allows for desiccation of the lesion with small energy bursts that will not harm the underlying bronchus [51, 52]. Removal of larger pieces of tissue may be achieved with biopsy forceps through the flexible bronchoscope. Use of the flexible bronchoscope may be useful for distal, smaller lesions in particular. These techniques may take a long time if the lesion is large and if there is a risk of bleeding (i.e., hemangioma or vascular lesion), the flexible bronchoscope is less able to control the bleeding.

When tracheal or bronchial stenosis is present, several modalities may be used via flexible bronchoscope. They include *balloon dilation*, laser and stent placement with or without application of medications such as mitomycin or steroids [39]. While traditionally a rigid bronchoscope is used, a larger flexible scope with a 2.0 mm working channel through an LMA can be used for angioplasty balloons [53]. Balloon dilation often needs to be repeated serially to achieve the final result and can be combined with the other dilating therapies. There are also risks of bleeding or airway rupture with this procedure.

The flexible bronchoscope may be used to *instill medications* directly to affected portions of the lung. This includes the already mentioned placement of epinephrine on a bleeding airway but also included placing mucolytics such as recombinant human DNase, n-acetylcysteine, hypertonic saline, or sodium bicarbonate to a mucus-plugged bronchus [39]. Additionally, medications such as surfactant may affectively be placed in the bronchial tubes [54].

Stent placement is typically thought of as a procedure done with a rigid bronchoscope. The flexible instrument, however, is able to deliver and/or check placement of a stent before it is expanded or finalized. There are three main types of stents: silicone, metal mesh, and biodegrad-

able. The flexible scope can ensure the patency of the airway after a stent is placed and can be used to check for complications such as stent slippage or formation of granulation tissue [39].

The flexible bronchoscope is able to identify the location of a bronchopleural fistula by placing an occluding balloon through the bronchoscope and inflating to see if the leak from the chest tube disappears [55]. Once the site of the fistula is known, the flexible bronchoscope can deliver methacrylate adhesive (airway glue) to the site of a persistent air leak from the bronchopleural fistula. The tube of glue is delivered in the working channel of the flexible bronchoscope and then delivered through the catheter out of the end of the bronchoscope once in place [56]. This technique is especially useful when the operative risk for the patient is too high.

Cryotherapy is a technically generaly reserved for adult patients. Many cryoprobes require a large channel for use. The cryoprobe, however, has been used to not only desiccate tissue mass, as in a granuloma, but also to freeze a mucus plug or blood clot and effectively remove it in one piece [57, 58].

The overall category of therapeutic indications is growing rapidly. The advent of newer tools such as the cryoprobe, EBUS/TBNA, and bronchial thermoplasty has already changed the way adult flexible bronchoscopy is performed. These tools are being reformulated for smaller people and smaller bronchoscopes. At the same time, bronchoscopes are improving with better optics, more maneuverability and larger working channels for the same size bronchoscope. Indications will change as tools advance.

Risks/Complications

Pediatric bronchoscopy is generally a safe and effective procedure for diagnosis and therapeutic management of a number of diseases. With any procedure, especially those requiring general anesthesia, there are risks that must be evaluated and minimized. Much care should be taken to determine that the patient has appropriate indications for bronchoscopy. Preparation is necessary to avoid unnecessary risk. Timing, location of procedure, and best anesthetic should be considered, appropriate and properly working tools should be gathered, and all personnel should be well-trained in bronchoscopy. When involved, trainees should be accompanied by staff experienced in teaching bronchoscopy.

Risks Associated with Anesthesia

Flexible bronchoscopy can be performed in multiple locations with varying levels of sedation/anesthesia. Although anesthetic medications each have their own side effect profile, symptoms associated with impaired ventilation, oxygenation, and airway irritation can be seen. General anesthesia is also associated with postoperative confusion, nausea and vomiting, and other systemic symptoms. In a large multisite prospective cohort of children who were sedated for various procedures performed outside of an operative room, hypoxemia, defined as oxygen desaturation below 90% for more than 30 seconds, was the most common complication [59]. Whereas children having flexible bronchoscopy often have indications of airway and pulmonary symptoms, this group were relatively healthy with less than 2% having preexisting airway or lung disease. Other rare complications in the cohort were stridor, laryngospasm, unexpected apnea, and aspiration [59].

In an attempt to limit laryngospasm and cough, topical analgesic, traditionally lidocaine, may be applied before and during the procedure to the vocal folds, carina, or both. When the bronchoscopy is beginning, the anesthesiologist must be attentive to the patient's level of sedation. Patients who are inadequately anesthetized are at risk for laryngospasm. The amount of lidocaine administered by the anesthesiologist and the bronchoscopist should be monitored closely. Although rare, lidocaine toxicity can result in seizures, and general anesthesia can lower the seizure threshold in those patients who are prone to them. Amitai and colleagues reported no complications after applying 3–8 mg/kg of topical lidocaine in 15 children [60]. A "spray-as-you-go"

approach is recommended for optimum effectiveness while limiting the overall lidocaine dose to a maximum of 3–5 mg/kg total during the procedure.

Multiple studies have shown association between number of anesthetic exposures in children less than 3 years of age and future cognitive ability and academic achievement [61, 62]. Although general anesthetics are not definitively causative, it may be appropriate to limit or delay procedures in young children when possible. Increased risk has been reported in children undergoing flexible bronchoscopy combined with other procedures above those undergoing flexible bronchoscopy alone [63]; however, the risk of performing those additional procedures under separate anesthetics was not evaluated.

Risks and Complications

A flexible bronchoscope occupies space in the airway of a child who even prior to the procedure has varying degrees of respiratory symptoms and impairment. Impaired ventilation during the procedure is therefore fairly unique to flexible bronchoscopy. The size of the scope, the size of the child's airway, and any airway device used for ventilation (laryngeal mask airway, tracheostomy, endotracheal tube) affect the amount the airway is obstructed. Small children have low functional reserve and the effect of the scope on ventilation and oxygenation is more dramatic. In children with a 4.0 mm inner diameter endotracheal tube, a 2.8 mm outer diameter bronchoscope will occlude the airway by 49–70%, significantly increasing the resistance to airflow [64]. Although it is tempting to choose the largest scope that will fit in the breathing tube, the indication for the bronchoscopy and the child's tolerance of airway occlusion should be considered. When bronchoscopes are introduced through the nares, most infants greater than or equal to 3 kg can breathe adequately around the 3.5 mm flexible bronchoscope, and infants greater than 1.5 kg can breathe around the 2.8 mm scope [65].

Because of these impairments to ventilation, hypoxemia is the most common complication reported during flexible bronchoscopy [63, 66, 67]. The definition of hypoxemia as a complication vary based on institutional reports. Some report if the hypoxemia prolongs the duration of the procedure [5] and others provide more quantifiable definitions such as SpO2 < 90% for 30 seconds of time [8]. Post-op hypoxemia is also common [66]. The technique of bronchoalveolar lavage necessarily washes surfactant out of selected segments of the lung, thereby predisposing to post-op atelectasis, which likely contributes to this post-op hypoxemia.

Airway irritation, airway edema, laryngospasm, and post-op stridor can be seen with general anesthesia but are also risks of the flexible bronchoscope irritating the child's airway mucosa. Rates of laryngospasm of 1–5% are reported in large cohorts [63, 66, 68]. Bronchospasm can occur from irritation to the airway and lung in this high-risk population. The bronchoscopy team should remember that poor airflow without wheezing may be from extreme bronchospasm, and the use of intraoperative albuterol can allow the procedure to continue. Low levels of cigarette smoke exposure can cause increased airway edema [69], although the effects on flexible bronchoscopy outcomes in children exposed to secondhand smoke are not known.

Vagal stimulation and cardiorespiratory complications including cardiac arrest are rare but significant complications from flexible bronchoscopy [63, 70]. Death is a rare complication in pediatric flexible bronchoscopy attributed to sepsis in the few reported cases [71, 72].

Bleeding is more common in adult bronchoscopy than general pediatric bronchoscopy. Rates of <5% are seen in diagnostic pediatric flexible bronchoscopy [68, 73]. Bleeding and hemoptysis are also indications for bronchoscopy, and the bronchoscopy team must be prepared for acute bleeding. This includes checking a complete blood chemistry and coagulation profile prior to the procedure, performing high-risk procedures in an appropriate location (the operating room), and having equipment to intubate the patient and access to drugs to stop bleeding immediately available. Epistaxis can be seen with laryngoscopy and flexible bronchoscopy [68, 73].

Pneumothorax is reported although rarely in diagnostic bronchoscopy with lavage [70, 74]. To minimize risk of pneumothorax, bronchoscopists are taught to instill low flow oxygen only when the scope is in large airways and to use CPAP but not positive pressure ventilation while the scope is wedged during BAL collection. When these guidelines are followed, and the airway is not manipulated with biopsy forceps or other tools, the cause of pneumothorax is not always clear.

Infection

Whenever a foreign object is introduced into the body, a risk of infection exists. Guidelines for cleaning and sterilizing bronchoscopes based on manufacturer recommendations must be employed, followed, and reevaluated regularly by those responsible for bronchoscopy programs. Bacteria can grow in wet and drying bronchoscopes after high-level disinfection [75], and outbreaks of multidrug-resistant bacteria have been reported from the use of contaminated bronchoscopes [76]. With strict adherence to guidelines, current sterilization techniques appear to adequately limit this risk in flexible bronchoscopy; however, ongoing study in this area is needed.

A theoretical risk of contamination of oral, nasal, and tracheal flora into the lower airways exists with flexible bronchoscopy. Nose and mouth commensal organisms can be found in cultures from BAL; however, the exact contribution from the flexible bronchoscope is not clear [77]. For example, seeding of laryngeal and tracheal secretions to the lower airways after repeated endoscopy is a theoretical cause of recurrent laryngotracheal papillomatosis spreading to lung parenchyma [78]. Decreasing risk in patients with these infections and in immunocompromised patients at risk of infection should be considered when determining the method of bronchoscopy. An endotracheal tube can be placed to minimize contact between these surfaces and the flexible bronchoscope prior to BAL acquisition. Postoperative fever >38 degrees Celsius can occur within 24 hours of bronchoscopy with lavage in approximately 50% of patients [79]. This is likely due to stimulation of pyrogens from BAL rather than true infection. In a prospective study, increased risk of postoperative fever was observed in younger children and those with abnormal bronchoscopy findings [79]. In immunocompetent children there was no bacteremia at the time of fever [79].

Risks in Critically Ill Children

Children with critical illness in the intensive care unit are at increased risk of procedures although often will have increased benefit. The risk of adverse events in the ICU are approximately 13%, with hypotension and hypoxemia the most common; however, only 2% of patients required intervention for these events [2]. Extracorporeal membranous oxygenation (ECMO) may be both an indication and a relative contraindication for flexible bronchoscopy. In general, children on ECMO can tolerate flexible bronchoscopy without significant pump flow rate or sweep gas flow changes [3]. Blood-tinged airway secretions and oozing are more common in this population (6–35%) both during and post-procedure [3, 80].

Risk of Therapeutic and Interventional Bronchoscopy

Therapeutic and interventional procedures have risk based on procedure and preoperative severity of illness. In adults, thermoplasty has risk of symptoms associated with airway irritation resulting in worsening asthma symptoms within 1 day of the bronchoscopy [81]. In a double-blind prospective control study, 8% of adults with severe asthma who had thermoplasty were hospitalized during the study protocol versus 2% of the subjects who received sham therapy; however, the other improvements due to the treatment of thermoplasty likely outweighed this risk [81].

Children who have had lung transplantation will likely have multiple surveillance and diagnostic bronchoscopies. Post-transplant is the most common indication for transbronchial biopsy, which is associated with a 0.8–3.4% risk of pneumothorax

in this population [82]. Pulmonary hemorrhage due to laceration can be a severe complication in children with lung transplantation occurring approximately 1–5% in this population [82].

Foreign body removal via flexible or rigid bronchoscopy has reported risk of pneumonia and when unsuccessful may require repeat surgery [83]. In a cohort of over 2000 pediatric cases of airway foreign body, hypoxemia was again the most common complication [84]; however, severe complications including death has been reported in multiple series [83–85]. In these cases, damage from the foreign body itself appeared to be the cause of the complications rather than the surgery, although this cannot be universally assumed. In one case series, increased rates of complications were associated with unwitnessed aspiration and infiltrates on preoperative chest radiograph [85].

See individual sections for specific risks of other interventional procedures.

Risks to Medical Team

The flexible bronchoscopy procedure has the potential to expose the bronchoscopy team to infected aerosols. The American College of Chest Physicians and American Association for Bronchology recommend all members of the bronchoscopy team employ "infection control" precautions including gown, gloves, mask, and eye shields [86]. N95 particulate respirator or higher-grade respiratory precautions is recommended if mycobacterial infection is suspected and increased precautions should be used for highly contagious organisms.

Flexible bronchoscopy is a typical diagnostic procedure to determine the cause of cough or other respiratory symptoms; therefore, children with communicable diseases including mycobacterial disease, pertussis, and influenza may be typical patients. Based on the differential diagnosis, appropriate workup including sputum culture, viral testing, tuberculin skin testing, etc., should be completed before bronchoscopy. Bronchoscopists should have a low threshold to perform bronchoscopy in a negative pressure room and to wear fitted masks that prevent aerosol exposure in high-risk patients. Hospital epidemiologists should be consulted if highly transmissible infections are isolated from BAL fluid.

Risk of Damage to Equipment

Flexible bronchoscopes are essential but expensive investments for bronchoscopy programs. Pediatric bronchoscopes are thin, fragile, and easily broken. The time and cost to repair the scopes can affect not only productivity of the program but patient care. Patients must be appropriately sedated to prevent them from biting the bronchoscope and bite blocks should be used. Bronchoscopes must be transported and stored carefully by qualified individuals. Biopsy forceps and other tools must be used carefully to limit wear and tear on the bronchoscopy channel that is a known risk of this equipment.

Conclusion

Bronchoscopy is an integral component of diagnosis of pediatric pulmonary disease and is used increasingly for therapeutic and interventional procedures. An often-quoted risk of bronchoscopy is obtaining the wrong answer or no answer from the procedure. Planning for adequate anesthesia, obtaining the proper equipment and team, and performing the appropriate tests will help create the circumstances to obtain the correct answer from the procedure. The importance of completing a "normal bronchoscopy" may be as useful as defining an abnormality.

The rare but statistical risk of serious complications including pneumothorax, cardiac complications, and cardiac arrest can affect the bronchoscopist in addition to the patient. Bronchoscopists should contemplate that indications for bronchoscopy are appropriate, the patient and their family provide adequate consent, and preparation for the procedure is thorough and repeatable. Problems with any component of flexible bronchoscopy should be reviewed by the program to continually limit risk.

When procedures are planned appropriately, bronchoscopy is generally a safe procedure. General anesthesia, while allowing the success of bronchoscopy, provides innate risk that should also be considered. Surgeons should be aware of pre-procedural risk, which may be increased in critically ill children. Severe complications including death, although statistically unlikely, do occur. As in all medical care, bronchoscopists should weigh the risks and benefits from the procedure and discuss these with patients and their families.

References

1. Faro A, Wood RE, Schecter MS, et al. Official American thoracic society technical standards: flexible airway endoscopy in children. Am J Respir Crit Care Med. 2015;191(9):1066–80.
2. Field-Ridley A, Sethi V, Murthi S, Nandalike K, Li ST. Utility of flexible fiberoptic bronchoscopy for critically ill pediatric patients: a systematic review. World J Crit Care Med. 2015;4(1):77–88.
3. Kamat PP, Popler J, Davis J, et al. Use of flexible bronchoscopy in pediatric patients receiving extracorporeal membrane oxygenation (ECMO) support. Pediatr Pulmonol. 2011;46(11):1108–13.
4. Peng YY, Soong WJ, Yee YS, Tsao PC, Yang CF, Jeng MJ. Flexible bronchoscopy as a valuable diagnostic and therapeutic tool in pediatric intensive care patients: a report on 5 years of experience. Pediatr Pulmomol. 2011;46(10):1031–7.
5. Soyer T. The role of bronchoscopy in the diagnosis of airway disease in children. J Thorac Dis. 2016;8(11):3420–6.
6. Midulla F, de Blic J, Barbato A, et al. Flexible endoscopy of paediatric airways. Eur Respir J. 2003;22:698–708.
7. Barbato A, Magarotto M, Crivellaro M, et al. Use of the paediatric bronchoscope, flexible and rigid, in 51 European centres. Eur Respir J. 1997;10:1761–6.
8. Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. Chest. 1998;114:133S.
9. Scellhase DE, Fawcett DD, Schutze GE, et al. Clinical utility of flexible bronchoscopy and bronchoalveolar lavage in young children with recurrent wheezing. J Pediatr. 1998;132(2):312–8.
10. Wood RE. The emerging role of flexible bronchoscopy in pediatrics. Clin Chest Med. 2001;22(2):311–7.
11. Boesch RP, Baughn JM, Cofer SA, Balakrishnan K. Trans-nasal flexible bronchoscopy in wheezing children: diagnostic yield, impact on therapy, and prevalence of laryngeal cleft. Pediatr Pulmonol. 2018;53:310–5.
12. Mancuso RF. Pediatric otolaryngology. Stridor in neonates. Pediatr Clin N Am. 1996;43(6):1339–55.
13. Erdem E, Gokdemir Y, Unal F, Ersu R, Karadag B, Karakoc F. Flexible bronchoscopy as a valuable tool in the evaluation of infants with stridor. Eur Arch Otorhinolaryngol. 2013;270(1):21–5.
14. Vijayasekaran D, Kalpana S, Ramachandran P, Nedunchelian K. Indications and outcome of flexible bronchoscopy in neonates. Indian J Pediatr. 2012;79(9):1181–4.
15. Najada AS, Dahabreh MM. Bronchoscopy findings in children with recurrent and chronic stridor. J Bronchology Interv Pulmonol. 2011;18(1):42–7.
16. Parnell FW, Brandenburg JH. Vocal cord paralysis: a review of 100 cases. Laryngoscope. 1970;80:1036–45.
17. Raoof S, Mehrishi S, Prakash UBS. Role of bronchoscopy in modern medical intensive care unit. Clin Chest Med. 2001;22(2):241–61.
18. Freitag L. Development of a new balloon catheter for management of hemoptysis with bronchofiberscopes. Chest. 1993;103:593.
19. Saw E, Gottlieb L, Yokoyama T, et al. Flexible fiberoptic bronchoscopy and endobronchial tamponade in the management of massive hemoptysis. Chest. 1976;70:589–91.
20. Bhat JI, Wani WA, Ahmad QI, et al. Flexible bronchoscopy in non-resolving pneumonia. Indian J Pediatr. 2017;84(9):681–4.
21. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. Pediatr Pulmonol. 1999;27:419–22.
22. Bauer ML, Lyrene RK. Chronic aspiration in children: evaluation of the lipid-laden macrophage index. Pediatr Pulmonol. 1999;28:94–100.
23. Abu-Hasan MN, Chesrown SE, Jantz MA. Successful use of bronchoscopic lung insufflation to treat left lung atelectasis. Pediatr Pulmonol. 2013;48(3):306–9.
24. Maggi JC, Nussbaum E, Babbitt C, Maggi FE, Randhawa I. Pediatric fiberoptic bronchoscopy as adjunctive therapy in acute asthma with respiratory failure. Pediatr Pulmonol. 2012;47(12):1180–4.
25. Sachdev A, Ghimiri A, Gupta N, Gupta D. Predecannulation flexible bronchoscopy in tracheaostomized children. Pediatr Surg Int. 2017;33(11):1195–200.
26. Midyat L, Cakit E, Kut A. Upper airway abnormalities detected in children using flexible bronchoscopy. Int J Pediatr Otorhinolaryngol. 2012;76(4):560–3.
27. Adil E, Gergin O, Kawai K, Ranbar R, Watters K. Usefulness of upper airway endoscopy in the evaluation of pediatric pulmonary aspiration. JAMA Otolaryngol Head Neck Surg. 2016;142(4):339–43.
28. Su SC, Masters IB, Buntain H, et al. A comparison of virtual bronchoscopy versus flexible bronchoscopy in the diagnosis of tracheobronchomalacia in children. Pediatr Pulmonol. 2017;52(4):480–6.
29. Sanchez MO, Greer MC, Masters IB, Chang AB. A comparison of fluoroscopic airway screening with

flexible bronchoscopy for diagnosing tracheomalacia. Pediatr Pulmonol. 2012;47(1):63–7.
30. Platnaris A, Lianou D, Kaditis AG. Recurrent tracheoesophageal fistula in children with repaired esophageal atresia and the usefulness of flexible bronchoscopy. Arch Bronconeumol. 2015;51(1):49–50.
31. Bush A, Pohunek P. Brush biopsy and mucosal biopsy. Am J Respir Crit Care Med. 2000;162:518–22.
32. Cokugras H, Akcakaya N, Seckin I, Camicoglu Y, Sarimurat N, Aksoy F. Ultrastructural examination of bronchial biopsy specimens from children with moderate asthma. Thorax. 2001;56:25–9.
33. Payne DNR, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma after treatment with oral prednisone. Am J Respir Crit Care Med. 2001;164:1376–81.
34. Payne DN, Rogers AV, Adelroth E, et al. Early thickening of the reticular basement membrane in children with difficult asthma. Am J Respir Crit Care Med. 2003;167:78–82.
35. Payne D, McKenzie SA, Stacey S, Misra D, Haxby E, Bush A. Safety and ethics of bronchoscopy and endobronchial biopsy in difficult asthma. Arch Dis Child. 2001;84:423–6.
36. Whitehead B, Scott JP, Helms P, et al. Technique and use of transbronchial biopsy in children and adolescents. Pediatr Pulmonol. 1992;12:240–6.
37. Scott JP, Higenbottam TW, Smyth RL, et al. Transbronchial biopsies in children after heart-lung transplantation. Pediatrics. 1990;86:698–702.
38. Fan LL, Kozinetz CA, Wojezak HA, Chatfield BA, Cohen AH, Rothenberg SS. Diagnostic value of transbronchial, thorascopic, and open lung biopsy in immunocompetent children with chronic interstitial lung disease. J Pediatr. 1997;131:565–9.
39. Eber E, Anton-Pacheco JL, de Blic J, et al. ERS statement: interventional bronchoscopy in children. Eur Respir J. 2017;50:1–19.
40. Goussard P, Gie RP, Kling S, et al. The diagnostic value and safety of transbronchial needle aspiration biopsy in children with mediastinal lymphadenopathy. Pediatr Pulmonol. 2010;45:1173–9.
41. Gibb E, Blount R, Lewis N, et al. Management of plastic bronchitis with topical tissue-type plasminogen activator. Pediatrics. 2012;130(2):e446–50.
42. Finer NN, Muzyka D. Flexible endoscopic intubation of the neonate. Pediatr Pulmonol. 1992;12:48–51.
43. Ramirez-Figueroa JL, Gochicoa-Rangel LG, Ramirez-San Juan DH, Vargas MH. Foreign body removal by flexible fiberoptic bronchoscopy in infants and children. Pediatr Pulmonol. 2005;40:392–7.
44. Tang LF, Xu YC, Wang YS, et al. Airway foreign body removal by flexible bronchoscopy: experience with 1027 children during 2000–2008. World J Pediatr. 2009;5:191–5.
45. Jayaraj AK, Jayaraj PK, Murugesh M, Aruchamy S, Yousefzadeh A, Siddiqui NT. Tracheal foreign body removal using flexible bronchoscopy in a pediatric patient. Am J Respir Crit Care Med. 2017;196(8):1071–2.
46. Hata A, Nakajima T, Ohashi K, et al. Mini grasping basket forceps for endobronchial foreign body removal in pediatric patients. Pediatr Int. 2017;59(11):1200–4.
47. Soong WJ, Tsao PC, Yee YS, Yang CF. Retrieval of tracheobronchial foreign bodies by short flexible endoscopy in children. Int J Pediatr Otorhinolaryngol. 2017;95:109–13.
48. Tenenbaum T, Kahler G, Janke C, Schroten H, Demiracka S. Management of foreign body removal in children by flexible bronchoscopy. J Bronchology Interv Pulmonol. 2017;24(1):21–8.
49. Mansour B, Elias N. Foreign body aspiration in children with the focus on the role of flexible bronchoscopy: a five year experience. Isr Med Assoc J. 2015;17(10):599–603.
50. Matsushita K, Uchida K, Otake K, et al. The "multiport airway adapter" in flexible bronchoscopy for peripheral bronchial foreign bodies in children. Int J Pediatr Otorhinolaryngol. 2015;79(12):2470–2.
51. Azizkhan RG, Lacey SR, Wood RE. Acquired symptomatic bronchial stenosis in infants: successful management using an argon laser. J Pediatr Surg. 1990;25:19–24.
52. Bagwell CE. CO2 laser excision of paediatric airway lesions. J Pediatr Surg. 1990;25:1152–6.
53. Xin Y, Wang G, Gao X, et al. Interventional bronchoscopy via laryngeal mask airway (LMA) under general anesthesia in children using adult flexible bronchoscope. Kawait Med J. 2016;48:317–22.
54. Nakamura CT, Ripka JF, McVeigh K, Kapoor N, Keens TG. Bronchoscopic instillation of surfactant in acute respiratory distress syndrome. Pediatr Pulmonol. 2001;31:317–20.
55. Baumann MH, Sahn SA. Medical management and therapy of bronchopleural fistulas in the mechanically ventilated patient. Chest. 1990;97:721–8.
56. Wood RE, Lacey SR, Azizkhan RG. Endoscopic management of large postresection bronchopleural fistulae with methacrylate adhesive (Super Glue). J Pediatr Surg. 1992;27:201–2.
57. Mathur PN, Wolf KM, Busk MF, et al. Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. Chest. 1996;110(3):718–23.
58. Zhang L, Yin Y, Zhang J, Zhang H. Removal of foreign bodies in children's airways using flexible bronchoscopic CO2 cryotherapy. Pediatr Pulmonol. 2016;51(9):943–9.
59. Cravero JP, Blike GT, Beach M, Gallagher SM, Hertzog JH, Havidich JE, et al. Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: report from the Pediatric Sedation Research Consortium. Pediatrics. 2006;118(3):1087–96.
60. Amitai Y, Zylber-Katz E, Avital A, Zangen D, Noviski N. Serum lidocaine concentrations in children during bronchoscopy with topical anesthesia. Chest. 1990;98(6):1370–3.

61. Hu D, Flick RP, Zaccariello MJ, Colligan RC, Katusic SK, Schroeder DR, et al. Association between exposure of young children to procedures requiring general anesthesia and learning and behavioral outcomes in a population-based birth cohort. Anesthesiology. 2017;127(2):227–40.
62. Backeljauw B, Holland SK, Altaye M, Loepke AW. Cognition and brain structure following early childhood surgery with anesthesia. Pediatrics. 2015;136(1):e1–12.
63. DeBoer EM, Prager JD, Kerby GS, Stillwell PC. Measuring pediatric bronchoscopy outcomes using an electronic medical record. Ann Am Thorac Soc. 2016;13(5):678–83.
64. Khan EK, Baker CD. Endotracheal or tracheostomy tube occlusion during pediatric flexible bronchoscopy. Pediatr Pulmonol. 2018;
65. Wood RE. In: Wilmott RW, Deterding RR, Li A, Ratjen F, Sly P, Zar HJ, et al., editors. Kendig's disorders of the respiratory tract in children. 9th ed: Elsevier; 2018. p. 134–46.
66. Carlens J, Fuge J, Price T, DeLuca DS, Price M, Hansen G, et al. Complications and risk factors in pediatric bronchoscopy in a tertiary pediatric respiratory center. Pediatr Pulmonol. 2018;53(5):619–27.
67. Schnapf BM. Oxygen desaturation during fiberoptic bronchoscopy in pediatric patients. Chest. 1991;99(3):591–4.
68. Nussbaum E. Pediatric fiberoptic bronchoscopy: clinical experience with 2,836 bronchoscopies. Pediatr Crit Care Med. A journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2002;3(2):171–6.
69. Strulovici-Barel Y, Omberg L, O'Mahony M, Gordon C, Hollmann C, Tilley AE, et al. Threshold of biologic responses of the small airway epithelium to low levels of tobacco smoke. Am J Respir Crit Care Med. 2010;182(12):1524–32.
70. Wood RE. Spelunking in the pediatric airways: explorations with the flexible fiberoptic bronchoscope. Pediatr Clin N Am. 1984;31(4):785–99.
71. Wagener JS. Fatality following fiberoptic bronchoscopy in a two-year-old child. Pediatr Pulmonol. 1987;3(3):197–9.
72. Picard E, Schlesinger Y, Goldberg S, Schwartz S, Kerem E. Fatal pneumococcal sepsis following flexible bronchoscopy in an immunocompromised infant. Pediatr Pulmonol. 1998;25(6):390–2.
73. Raine J, Warner JO. Fibreoptic bronchoscopy without general anaesthetic. Arch Dis Child. 1991;66(4):481–4.
74. Rock MJ. The diagnostic utility of bronchoalveolar lavage in immunocompetent children with unexplained infiltrates on chest radiograph. Pediatrics. 1995;95(3):373–7.
75. Ofstead CL, Quick MR, Wetzler HP, Eiland JE, Heymann OL, Sonetti DA, et al. Effectiveness of reprocessing for flexible bronchoscopes and endobronchial ultrasound bronchoscopes. Chest. 2018;154(5):1024–34.
76. Alipour N, Karagoz A, Taner A, Gaeini N, Alipour N, Zeytin H, et al. Outbreak of hospital infection from biofilm-embedded pan drug-resistant pseudomonas aeroginosa, due to a contaminated bronchoscope. J Prev Med. (Wilmington). 2017;2(2):1.
77. Reynolds HY. Bronchoalveolar lavage and other methods to define the human respiratory tract milieu in health and disease. Lung. 2011;189(2):87–99.
78. Kramer SS, Wehunt WD, Stocker JT, Kashima H. Pulmonary manifestations of juvenile laryngotracheal papillomatosis. AJR Am J Roentgenol. 1985;144(4):687–94.
79. Picard E, Schwartz S, Goldberg S, Glick T, Villa Y, Kerem E. A prospective study of fever and bacteremia after flexible fiberoptic bronchoscopy in children. Chest. 2000;117(2):573–7.
80. Prentice E, Mastropietro CW. Flexible bronchoscopy for children on extracorporeal membrane oxygenation for cardiac failure. Pediatr Crit Care Med. A journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2011;12(4):422–5.
81. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade LM, Shah PL, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010;181(2):116–24.
82. Wong JY, Westall GP, Snell GI. Bronchoscopic procedures and lung biopsies in pediatric lung transplant recipients. Pediatr Pulmonol. 2015;50(12):1406–19.
83. Roberts CA, Carr MM. Morbidity and mortality in children undergoing bronchoscopy for foreign body removal. Laryngoscope. 2018;128(5):1226–9.
84. Boufersaoui A, Smati L, Benhalla KN, Boukari R, Smail S, Anik K, et al. Foreign body aspiration in children: experience from 2624 patients. Int J Pediatr Otorhinolaryngol. 2013;77(10):1683–8.
85. Sjogren PP, Mills TJ, Pollak AD, Muntz HR, Meier JD, Grimmer JF. Predictors of complicated airway foreign body extraction. Laryngoscope. 2018;128(2):490–5.
86. Mehta AC, Prakash UB, Garland R, Haponik E, Moses L, Schaffner W, et al. American College of Chest Physicians and American Association for Bronchology [corrected] consensus statement: prevention of flexible bronchoscopy-associated infection. Chest. 2005;128(3):1742–55.

7 Bronchoalveolar Lavage: Sampling Methods

Greta Di Mattia, Giulia Lais, and Fabio Midulla

Bronchoalveolar lavage (BAL) is a useful and safe diagnostic and therapeutic technique used to recover cellular and noncellular components from the bronchial and alveolar epithelium. It consists of the instillation and immediate suction of pre-warmed sterile 0.9% saline solution in a selected bronchus. Although multiple authors have described the clinical utility of BAL in numerous lung diseases, universal guidelines on technical aspects in children are still lacking and rely mainly on tasks forces [1–3].

Techniques and Wedge

Two techniques are currently used to recover the epithelial lining fluid (ELF) from the airways: nonbronchoscopic and bronchoscopic BAL.

Nonbronchoscopic BAL is mainly used to evaluate the presence of infectious agents in mechanically ventilated patients in intensive care units. A catheter (size 4–8 French) is inserted through an endotracheal tube and is blindly wedged into a distal airway. Although this procedure is performed without visualizing the lavage site, putting children in the supine position with their head turned to the left helps reaching the right lung [4].

Bronchoscopic BAL is performed through the injection of pre-warmed sterile saline solution into the working channel of a flexible bronchoscope, the tip of which is inserted into a bronchus with a matching diameter. The diameter of the bronchoscope is established basing on the patient's age: general recommendations for sizing include bronchoscopes with external diameters of 2.8–3.7 mm and a working channel of 1.2 mm for children younger than 6 years of age, and with external diameters of 4.0–5.2 mm and a working channel of 2.0–2.2 mm for children older than 6 years of age [5]. These recommendations can be adjusted based on patient needs, i.e., if there is a clinical indication for a larger scope with a larger working channel this could be used on a younger patient keeping in mind the ability of the airway to accommodate along with patient safety.

In neonates, flexible bronchoscopy is performed with the smallest bronchoscopes with an external diameter of 2.2 mm. However, this kind of instrument does not have a suction channel. Thus, only nonbronchoscopic BAL can be used to recover ELF in this age group, and the procedure can only be performed in intubated neonates [6, 7].

Site of Lavage

The preferred lavage site must be decided according to the type of lung disease and the extent of lung involvement. The recommenda-

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_7

tion is to perform a BAL of the right middle lobe or of the lingula in the case of diffused lung disease because, those being the smallest lobes, about 20% more fluid can be recovered when compared to the lower lobes. Furthermore, the lower lobes are difficult to wedge with the bronchoscope and more fluid is needed to recover a representative aliquot of the ELF. In general, in diffuse interstitial lung disease, there is an excellent interlobar correlation in the recovered fluid. Thus, performing the lavage of one lobe should be sufficient to obtain information representative for the whole lung [1, 2]. However, in patients with cystic fibrosis (CF), lavages should be performed in multiple sites of both lungs because the bacterial colonization could differ within different areas of the airways. In particular, in patients with CF, BAL samples should be obtained from different lobes: from the right middle lobe, from the lingula, and from the most affected lobe [1, 8, 9]. Finally, in the case of a localized disease, BAL must be performed on the affected lobe or segment, radiologically or endoscopically targeted. In order to avoid contamination, BAL must precede any other bronchoscopic procedure [1, 3].

Type and Amount of Solution

The solution utilized for BAL is sterile 0.9% (normal) saline solution, at room temperature or pre-warmed at body temperature (37 °C). Saline solution warmed at body temperature is preferred as it is associated less frequently with cough, bronchospasm, and lung function deterioration and because it offers better fluid recovery when compared to fluid at room temperature [10, 11]. The amount of recovered ELF depends on the volume of solution that is first injected. Various protocols may be used to calculate the amount of saline and the number of aliquots needed to obtain representative samples of the alveolar spaces. The following three methods are the most used worldwide. Riedler et al. suggested a calculation of the BAL volume based on the body weight: three aliquots of 1 ml/Kg in children weighting <20 Kg and three aliquots of 20 ml in children >20 Kg [12]. Supporting this method, Ratjen et al. demonstrated that adjusting the amount of injected saline according to body weight in children 3–5 years allows to recover constant fractions of the ELF [13]. Midulla et al. prefer the collection of two to four aliquots of the same volume according to the patient's age and irrespective of body weight: 10 ml per aliquot for children up to 6 years of age and 20 ml per aliquot for children older than 6 years of age [5]. Finally, De Blic et al. suggested a BAL volume calculation based on the child's functional residual capacity (FRC), using a maximum volume of 10% of the child FRC, with fractions of 5–20 ml according to the patient's size [14]. In larger adolescent similar to adults, individual aliquots up to 60–80 ml are often used.

Fluid Recovery

After wedging the flexible bronchoscope into the selected bronchus and while maintaining this position, sterile pre-warmed saline solution is instilled through the working channel using a syringe; each instillation should be followed by the injection of air, to empty the channel's dead space. After the injection of the solution, fluid may be recovered by manual or mechanical suction, using pressures in the range 3.33–13.3 kPa (25–100 mmHg). Manual aspiration of the fluid with a syringe is preferred over mechanical suctioning into a collection trap as the suctioning pressure may be more easily adjusted, and that is important in preventing the collapse of the distal airways. In fact, an excessive negative pressure could lead to airway collapse beyond the tip of the bronchoscope with difficult fluid recovery, or to bronchial epithelial surface damage, further resulting in a bloody BAL. There is no consensus over the correct timing between saline injection and subsequent fluid suctioning: a delay of a few seconds may allow the saline to better mix with cellular and noncellular components of the ELF. However, a part of the instilled fluid is reabsorbed by the lymphatics during the procedure, suggesting not to wait too long before suctioning [1, 2, 15]. In general, BAL is considered accept-

able if more than 40% of the instilled fluid is recovered and if it contains a few epithelial cells (except for the first sample). Fluid recovery is lower in patients with obstructive lung disease [1, 15]. If three aliquots of fluid are instilled and recovered, the first one is representative of the bronchial space: it contains a lower number of cells, with more neutrophils and fewer lymphocytes than the subsequent ones and should be used for microbiology. The subsequent two fractions recover fluid from the alveolar space and should be used for cytology and to study the non-cellular components (solutes, inflammatory markers, etc.) [15, 16].

References

1. de Blic J, Midulla F, Barbato A, Clement A, Dab I, Eber E, et al. Bronchoalveolar lavage in children. ERS task force on bronchoalveolar lavage in children. European Respiratory Society. Eur Respir J. 2000;15:217–31.
2. Klech H, Pohl W. Technical recommendations and guidelines for bronchoalveolar lavage (BAL). Report of the European Society of Pneumology Task Group. Eur Respir J. 1989;2:561–85.
3. Faro A, Wood RE, Schechter MS, Leong AB, Wittkugel E, Abode K, et al. Official American Thoracic Society technical standards: flexible airway endoscopy in children. Am J Respir Crit Care Med. 2015;191:1066–80. https://doi.org/10.1164/rccm.201503-0474ST.
4. Heaney LG, Stevenson EC, Turner G, Cadden IS, Taylor R, Shields MD, et al. Investigating paediatric airways by non-bronchoscopic lavage: normal cellular data. Clin Exp Allergy. 1996;26:799–806.
5. Midulla F, Nenna R, Eber E. Bronchoalveolar lavage. In: Midulla F, Eber E, editors. ERS handbook: paediatric respiratory medicine. Sheffield: The European Respiratory Society; 2013. p. 140–5.
6. Koumbourlis AC, Kurland G. Nonbronchoscopic bronchoalveolar lavage in mechanically ventilated infants: technique, efficacy and applications. Pediatr Pulmonol. 1993;15:257–62.
7. Alpert BE, O'Sullivan BP, Panitch HB. Non-bronchoscopic approach to bronchoalveolar lavage in children with artificial airways. Pediatr Pulmonol. 1992;13:38–41.
8. Gutierrez JP, Grimwood K, Armstrong DS, Carlin JB, Carzino R, Olinsky A, et al. Interlobar differences in bronchoalveolar lavage fluid from children with cystic fibrosis. Eur Respir J. 2001;17:281–6.
9. Gilchrist FJ, Salamat S, Clayton S, Peach J, Alexander J, Lenney W. Bronchoalveolar lavage in children with cystic fibrosis: how many lobes should be sampled? Arch Dis Child. 2011;96:215–7. https://doi.org/10.1136/adc.2009.177618.
10. Pingleton SK, Harrison GF, Stechschulte DJ, Wesselius LJ, Kerby GR, Ruth WE. Effect of location, pH, and temperature of instillate in bronchoalveolar lavage in normal volunteers. Am Rev Respir Dis. 1983;128:1035–7. https://doi.org/10.1164/arrd.1983.128.6.1035.
11. Bums OM, Shure D, Francoz R, Kalafer M, Harrell J, Witztum K, et al. The physiological consequences of saline lobar lavage in healthy human adults. Am Rev Respir Dis. 1983;127:695–701.
12. Ratjen F, Bruch J. Adjustment of bronchoalveolar lavage volume to body weight in children. Pediatr Pulmonol. 1996;21:184–8. https://doi.org/10.1002/(SICI)1099-0496(199603)21:3<184::AID-PPUL6>3.0.CO;2-Q.
13. Riedler J, Grigg J, Stone C, Tauro G, Robertson CF. Bronchoalveolar lavage cellularity in healthy children. Am J Respir Crit Care Med. 1995;152:163–8. https://doi.org/10.1164/ajrccm.152.1.7599817.
14. de Blic J, McKelvie P, Le Bourgeois M, Blanche S, Benoist MR, Scheinmann P. Value of bronchoalveolar lavage in the management of severe acute pneumonia and interstitial pneumonitis in the immunocompromised child. Thorax. 1987;42:759–65.
15. Midulla F, Nenna R. Bronchoalveolar lavage: indications and applications. In: Priftis KN, Anthracopoulos MB, Eber E, Koumbourlis AC, Wood RE, editors. Paediatric bronchoscopy. Basel: Karger; 2010. p. 30–41.
16. Pohunek P, Pokorná H, Stríz I. Comparison of cell profiles in separately evaluated fractions of bronchoalveolar lavage (BAL) fluid in children. Thorax. 1996;51:615–8.

Bronchoalveolar Lavage: Cytology

8

Jennifer Pogoriler

Cell counts and the cytologic assessment of specific cell types are helpful in determining whether fluid obtained from a bronchoalveolar lavage procedure is an adequate representation of the alveolar spaces and whether it has a markedly abnormal distribution of inflammatory cells, although only in a subset of cases are the findings specific for a given lung disease [1]. Outside of identifying infectious organisms, bronchoalveolar lavage in children is most helpful in diagnosing alveolar hemorrhage, some subtypes of surfactant deficiencies, and sometimes aspiration.

Cell Types, Adequacy, and Specimen Handling

Ideally the bronchoalveolar lavage process samples predominantly cells and material within the airspaces of terminal bronchioles and alveoli. The presence of macrophages with abundant, variably foamy cytoplasm (Figs. 8.1 and 8.2a) is considered indicative of this location. In healthy patients, smaller numbers of other inflammatory cells, predominantly lymphocytes, are also present. In addition, small numbers of epithelial cells are virtually always present. Ciliated epithelial cells are the predominant cell type lining bronchi and bronchioles (Fig. 8.2a), and these are often present in small numbers in bronchoalveolar lavage fluid (Fig. 8.2b). Healthy alveoli are lined by type 1 (flat) pneumocytes (Fig. 8.2a), with more abundant reactive type 2 pneumocytes present in injured alveoli. Neither of these alveolar epithelial cell types are commonly recognized in cytology preparations, although reactive type 2 cells may be seen in diffuse alveolar damage.

Because the bronchoscope passes through the oral cavity and upper airway, squamous cells may be carried over from these areas (Fig. 8.3a). Squamous metaplasia may be seen

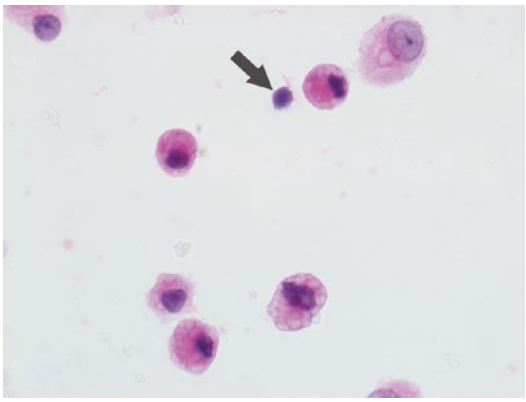

Fig. 8.1 Alveolar macrophages are recognized by their abundant, variably foamy cytoplasm. In an adequate sample from a healthy patient they are the predominant cell type. In this figure all the cells are macrophages except the one with an arrow, which is a lymphocyte

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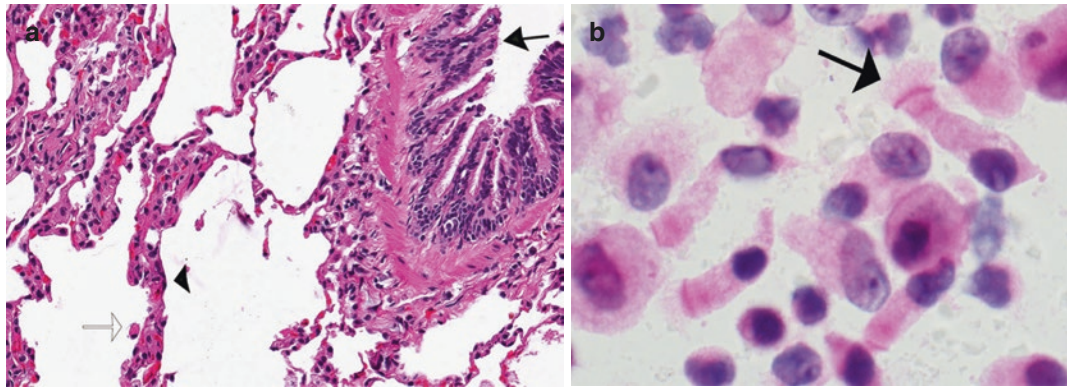

Fig. 8.2 (**a**) In this H&E-stained section of lung, the bronchiole at upper right is lined by ciliated epithelial cells (arrow) with rare macrophages (white arrow) within the alveolar spaces. The alveoli are lined predominantly by flattened epithelial cells (arrowhead). (**b**) Several ciliated epithelial cells are present and are recognized in bronchoalveolar fluid by their rectangular shape with a nucleus at the base and delicate cilia at the apex (arrows)

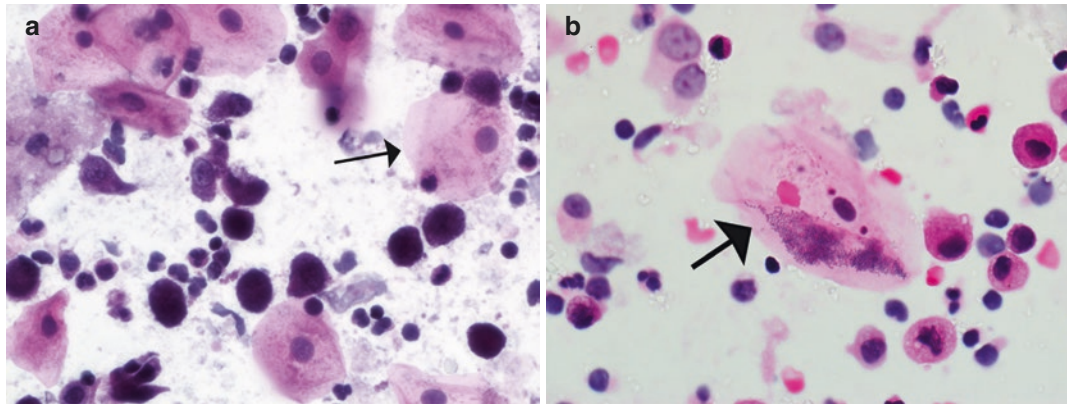

Fig. 8.3 (**a**) In this specimen, numerous squamous cells (arrows) are present with small nuclei and abundant dense pink cytoplasm. Their relative frequency suggests significant upper airway contamination. (**b**) Numerous coccoid bacteria coat this squamous cell

in large airways with severe inflammation, as in bronchiectasis, but is not a component of small airway disease in children and should be regarded as an indication of upper airway contamination. Oral squamous cells may be coated in bacteria (Fig. 8.3b), and it is not uncommon for other oral flora, such as yeast, to be present in specimens with abundant squamous cells. Recognition of oral or airway contamination is important since the inflammatory cells that are present may be derived from these compartments rather than from the alveolar spaces.

Extracellular material that is present may include mucous, which is generally faintly basophilic (purple) on hematoxylin and eosin stains, eosinophilic proteinaceous globules or granular material, or rarely necrotic debris. While this extracellular material may obscure the morphology of the cells or, in the case of abundant mucous, suggest airway contamination, it may also contribute to a diagnosis, as in pulmonary alveolar proteinosis.

Although the results of cytology and cell counts are often considered together, they are

typically performed in separate laboratories. Cell counts are usually performed by a hematology laboratory, similar to other body fluids. Some automated instruments for evaluating white blood cells are not approved for bronchoalveolar lavage fluid because of technical problems that can arise from the presence of mucous or from incorrect automated identification of epithelial cells. Therefore, in contrast to blood and other fluids, cell counts for bronchoalveolar lavage may be performed manually by a technologist using fluid deposited on a grid. Most hematology laboratories provide a total number of white blood cells in units per microliter, total number of red blood cells per microliter, and a differential with the percentage of each type of inflammatory cell (this excludes the epithelial cells).

In contrast to other body fluids, the concentration of cells in bronchoalveolar lavage specimens is somewhat dependent on the volume of saline infused and on the recovery. Therefore, reference ranges even in adults should only be depended upon if a standardized technique is used both for the procedure itself and the preparation [2]. There is some variation in the distribution of cell types present depending on whether or not the first aliquot is intermixed with subsequent aliquots (the first aliquot often has more epithelial cells and neutrophils) [3] as well as variation in cell type distribution between older and younger healthy adult subjects [4]. Small series have suggested that reference ranges for children are roughly similar to those for adults or that they may have slightly higher lymphocyte or neutrophil populations [5–7]. Given the scarcity of data, laboratories may not provide a definitive reference range for either total cell numbers or the differential; however, in a sample without significant upper airway contamination, macrophages usually make up somewhere around 80–90% of cells, with lymphocytes making up the majority of the remainder. One practical approach has been to consider as abnormal >20% lymphocytes, >10% neutrophils, and > 2% eosinophils because these numbers are widely outside any reference range (1). Adult guidelines use >15% lymphocytes, >3% neutrophils, and > 1% eosinophils [8].

Cytology examination is performed in a pathology laboratory – either by general pathologists or dedicated cytopathologists. A special fixative is added to the fluid to preserve cell structure, and a cytocentrifuge is used to concentrate and evenly spread a monolayer of cells across the slide. After drying, a range of routine and special stains can be used for cytologic evaluation. Routine stains in our laboratory include hematoxylin and eosin (H&E) and Papanicolaou (Pap) stain but other, equally effective stains may be used. In general, the same cell types and extracellular material are identified with all these stains but with different color characteristics, and the choice is dependent on local practice. While the range of cells present and their relative frequency is noted by the pathologist, dedicated counts are generally not performed.

Guidelines for specimen adequacy for cytologic evaluation have been established for bronchoalveolar lavage fluid in adults with interstitial lung disease [9]. Any specimen with a clear pathologic diagnosis is considered adequate regardless of other features. Otherwise, criteria for an unsatisfactory specimen include

1. Too few alveolar macrophages (<10 per high power field)
2. Excessive epithelial cells (>5%)
3. Mucopurulent exudate
4. Numerous red blood cells due to trauma during the procedure (in addition to at least one other criteria)
5. Degenerative changes or artifacts obscuring cell identity

In general, these guidelines address whether there are sufficient cells to adequately evaluate the alveolar milieu, whether there is upper airway/oral contamination by epithelial cells or degenerative changes. Some criteria, such as absence of mucopurulent exudate, are relevant specifically to evaluating chronic interstitial lung diseases, since this finding may be seen in adequate specimens from patients with acute pneumonia.

In the presence of abundant mucous and/or squamous cells to suggest upper airway or bron-

chial contamination, the significance of increased neutrophils in the differential or an increased cell count is uncertain. Increased neutrophils are often seen in patients with cystic fibrosis and can be seen in aspiration, diffuse alveolar damage, or following intubation [10]. However, in the appropriate context, if a specimen otherwise appears to be adequate, the presence of abundant neutrophils is consistent with acute infection. Ideally a source would be best identified by culture or viral PCR; however, cell counts and differential may be helpful in suggesting an etiology. Both increased total white blood cell numbers and percent of neutrophils have been reported in adult patients with either viral or bacterial pneumonia, with both total white blood cells and neutrophils more markedly elevated in bacterial pneumonia [11], but clear cutoffs are not established.

In healthy patients, eosinophils are relatively rare. Slightly elevated counts are often seen in asthma, infantile wheeze, and cystic fibrosis [10]. A cutoff of 25% has been suggested in adults as diagnostic for eosinophilic pneumonia [12]. Some reports suggest a lower cutoff of 20% for children [13]. Any of these numbers would suggest that eosinophils are the most prominent nonmacrophage intra-alveolar component. Rarely numbers this high may also be seen in hypereosinophilic asthma, and BAL does not provide a mechanism to distinguish between airway and alveolar eosinophils. Rarely patients with biopsy demonstration of prominent eosinophils have had a lower percentage (2–4%) in BAL fluid [14].

Markedly elevated lymphocyte subsets are also unusual and suggestive of underlying interstitial lung disease. Increased lymphocytes have been reported in children with hypersensitivity pneumonitis [15] but may also be present in other interstitial lung diseases with chronic inflammatory infiltrates including follicular bronchitis, sarcoidosis, and lymphocytic interstitial pneumonitis [1]. In patients who are post lung transplant or bone marrow transplant, abnormal lymphocyte numbers are concerning but do not distinguish between infection and rejection or graft versus host disease.

Flow Cytometry

Flow cytometry can be performed to better characterize specific lymphocyte populations. Guidelines in adults suggest that it be used in patients with a BAL lymphocytosis [8] but experience in pediatrics is relatively limited. The same caveats regarding adequacy and contamination apply as in general cell counts. Normal reference ranges for lymphocyte subsets in children are not well established. They may have a higher number of CD8-positive T cells, resulting in a lower CD4/CD8 ratio than in adults [5].

Most classically, the ratio of helper T cells (CD4 positive) to suppressor T cells (CD8 positive) has been reported to be increased in patients with sarcoidosis and decreased in patients with hypersensitivity [8]; however these abnormal ratios may not be valid in children due to an underlying difference in lymphocyte subsets in healthy children compared to those reported in adults [6, 15].

Special Stains for Cytology

Prussian Blue

Red blood cell breakdown results in the formation of hemosiderin, an iron storage complex, in macrophages. It has a golden-brown pigment, and, when present in large quantities is apparent on routinely stained cytology slides (Fig. 8.4a). However, other brown pigments, often inhaled, may be present, and in small quantities hemosiderin is less obvious. The special stain Prussian blue is used for more sensitive and specific evaluation of hemosiderin. The Prussian blue stain only highlights hemosiderin and does not stain iron in fresh red blood cells or some other unusual breakdown pigments such as hematoidin. In both BAL and biopsy specimens Prussian blue staining allows distinction between acute, procedure-related bleeding and true bleeding that occurred prior to instrumentation, and it allows detection of previous hemorrhage in a patient who is no longer actively bleeding. However, it is not sensitive in the setting of a

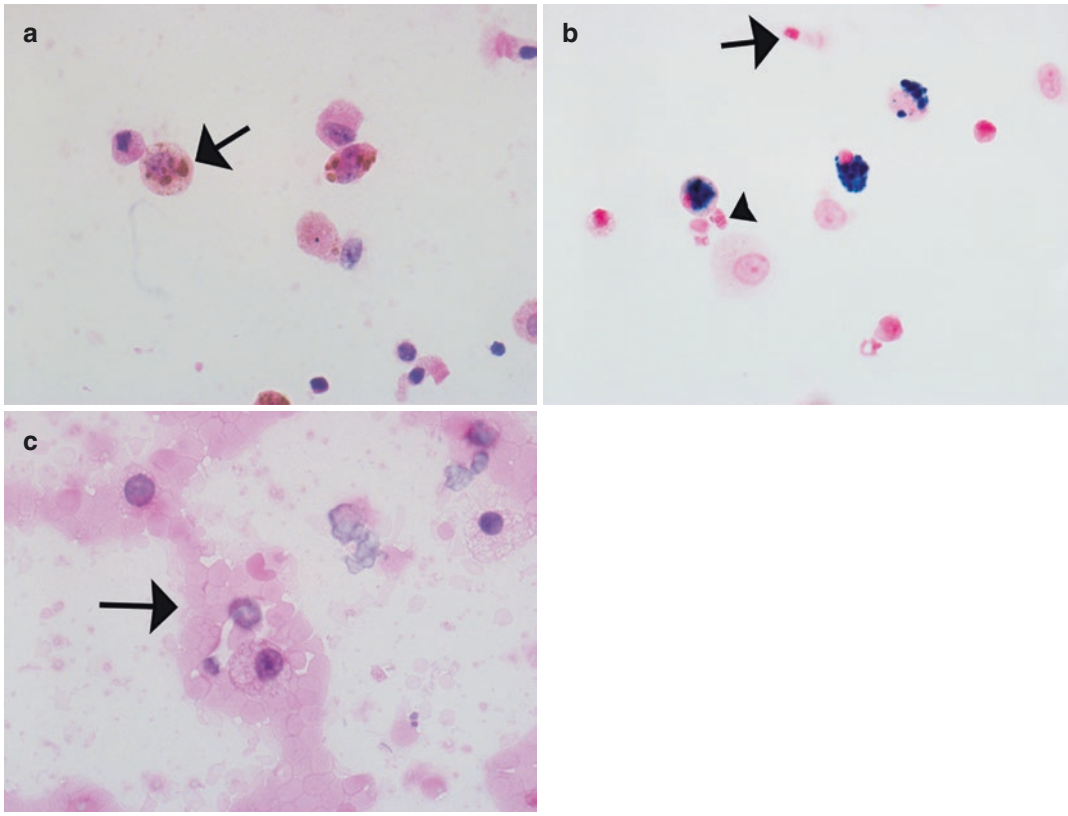

Fig. 8.4 (**a**) Globules of golden-brown pigment (arrow) are present in many macrophages in this patient with idiopathic pulmonary hemosiderosis. (**b**) The extent of hemosiderin is highlighted by Prussian blue stain showing that the majority of macrophages are positive. Smaller cells that are present are not included in the evaluation – for example, a ciliated epithelial cell (arrow) and neutrophil (arrowhead). (**c**) In this patient with an acute hemorrhagic event, numerous red blood cells (pink and anucleate) are present clustered around the nucleated cells. Prussian blue stain was negative due to the short time course preceding lavage

single acute bleeding event until at least several days have passed.

The time course of hemosiderin accumulation and clearance is poorly established. Few case reports of acute hemorrhage in infants with multiple bronchoalveolar lavages suggest that hemosiderin laden macrophages first appear at 50 hours after hemorrhage and may be cleared by several weeks [16]. More detailed time-course studies in mice demonstrate that although hemosiderin appears within several days, it peaks at approximately one week and then decreases over several weeks. It then persists indefinitely at low levels [17]. These models and case reports have been taken from healthy lungs, and it is unknown whether clearance from lungs with fibrosis or other active disease is altered.

Hemosiderin-laden macrophages are usually estimated as a percentage of total macrophages. In contrast to oil-red-O staining (see below), macrophages with any degree of iron staining are considered positive, as this has been shown to correlate well with more time-consuming and complex methods of quantification [18]. Scattered hemosiderin-laden macrophages may be present in any patient without specific clinical significance. Significantly elevated numbers may be present in any condition leading to increased red blood cells in the alveolar spaces, including heart failure, pulmonary hypertension, aspiration of blood or upper airway bleeding, infarction, severe infection, or diffuse alveolar damage. Precise cutoff values for "elevated" are not well established, but one small study of pediatric patients

with a clinical diagnosis of idiopathic hemosiderosis found a mean of 56% in comparison to "other" patients with a mean of 7% [19]. However, markedly elevated counts can be present in other conditions, notably in immunocompromised patients or those with diffuse alveolar damage [18, 20]. If these conditions are clinically excluded, the presence of significant numbers of hemosiderin-laden macrophages is consistent with pulmonary hemosiderosis.

Oil-Red-O

The oil-red-O stain highlights lipids in intracellular macrophages. Although commonly interpreted as aspiration, this stain does not distinguish between exogenous lipid and endogenous lipid such as in surfactant. All patients have some degree of lipid in macrophages, usually as fine scattered granules (Fig. 8.5). While markedly increased lipid accumulation can be seen in clinically documented aspiration, histologically foamy (lipid laden) macrophages are classically seen in lung biopsies with obstruction (endogenous lipoid pneumonia) as well as in pulmonary alveolar proteinosis. Fat may also be present in the lung due to fat embolism in sickle cell disease, and an increased lipid-laden index may be present in these patients [21, 22] as well as in those receiving parenteral nutrition.

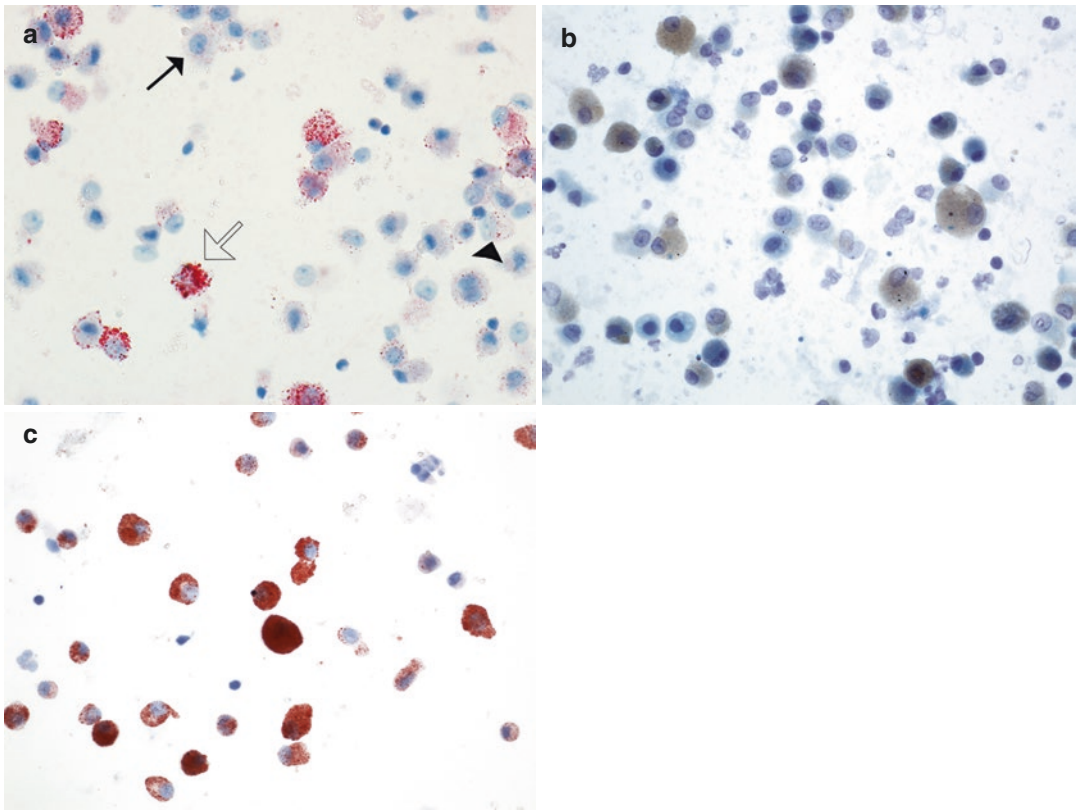

Fig. 8.5 (**a**) In this oil-red-O stain, fine granules (arrows) are present in the majority of macrophages, which would be considered entirely negative. Larger globules may be graded, most commonly on a scale of 1 (arrowhead) to 4 (white arrow) to calculate a lipid-laden macrophage index. (**b**) In this pap stain specimen from a patient with a history of cigarette, marijuana, and e-cigarette use, fine granular brown pigment can be seen corresponding to inhaled pigmented material. There is some variation in macrophage size, but they are not noticeably foamy. (**c**) Oil-red-O stain of patient with a history of cigarette, marijuana, and e-cigarette use shows abundant lipid-laden macrophages

Recently, abundant lipid-laden macrophages have been reported in some patients with a history of e-cigarettes (vaping) [23, 24] (Fig. 8.5b, c), often in combination with increased neutrophils. Lung biopsy of patients with vaping-induced lung toxicity have also shown lipoid pneumonia [25] in rare cases; however other patterns of injury are much more commonly reported, and not all patients with a history of vaping have increased lipid [23]. Oil-red-O has not traditionally been performed in adult institutions at the same rate as in pediatric samples, and the sensitivity and specificity of this finding for vaping is currently unknown.

Scoring of oil-red-O stain is classically performed as a combination of number of macrophages staining and their intensity. The most commonly suggested system evaluates 100 macrophages, and each is given a score of 0–4 based on the degree of cytoplasmic lipid (1 = up to ¼ opacification, 2 = up to ½ opacification, 3 = up to ¾ opacification, 4 = greater than ¾ opacification, or an alternative system where 1 = few individual droplets, 2 = many individual droplets, 3 = confluent droplets with nucleus visible, 4 = confluent droplets obscuring the nucleus.). The total score of the lipid laden macrophage index (LLMI) therefore theoretically ranges from 0–400 [26, 27]. Given the time-consuming nature of this type of analysis and its lack of reproducibility, simplified variants have been suggested [28, 29]. Alternatively, some publications have used any degree of oil-red-o staining and reported total percentage of cells [30], and at our own institution we report a roughly estimated percentage of macrophages with "marked" lipid accumulation (those equivalent to a score of 4). There are no thorough studies comparing these methodologies, but small reports have not suggested that simplified versions are inferior. Some studies have also used tracheal aspirates rather than bronchoalveolar lavage, and it is unknown whether the LLMI score may differ between the locations with differential sampling of the more proximal airways [31].

Early reports in pediatric patients suggested good sensitivity and specificity when populations were limited to those with clinically evident aspiration and those with no clinical evidence of aspiration [26] with a cutoff score of 72. However, in another study a mean LLMI of 60 was seen in healthy children and 119 in children with non-aspiration-related pulmonary disease, suggesting that a LLMI that is elevated above background levels is not specific [32]. Other publications have also shown greater overlap, particularly between children with aspiration and those with non-aspiration pulmonary disease [33], with a significantly higher best cutoff value in this scenario of 195. A recent report with impedance testing showed no significant correlation between LLMI and number of reflux events, amount of reflux or esophagitis. However, higher LLMIs were seen in patients without symptomatic improvement following fundoplication [34].

Some variation in the cutoffs may be due to institutional staining methodologies resulting in different intensities of red staining in the cytoplasm. This has not been adequately studied, although ranges of reported normal have up to a tenfold variation between institutions [35], suggesting that this is a significant issue and that, at a minimum, a normal range should be established within each institution if an index is to be calculated. However, at least a subset of the variability appears to be due to interobserver variability among pathologists looking at the same slide and even intraobserver variability [28, 36] with some poor agreement on repeat scoring of samples. In Fig. 8.5, it is clear that there is subjectivity to determining which cells would be 0 vs 1, 1 vs 2, 2 vs 3, etc. While many institutions will calculate a LLMI, many pathologists feel that provision of a specific number implies a misleading degree of objectivity and precision.

In general, therefore, a very high LLMI (or equivalent simplified quantification) in a patient with a suspicion of aspiration would support that diagnosis, while a very low LLMI would make it unlikely. However, in the context of other known pulmonary diseases, a high LLMI is not specific enough to suggest this as an additional diagnosis. All these interpretations require a degree of familiarity with an institution's usual values and

appreciation that this is a general estimate always reliant on subjective evaluation.

Special Stains for Pulmonary Alveolar Proteinosis

General categories of surfactant disorders include autoimmune pulmonary alveolar proteinosis (PAP) due to autoantibodies to GM-CSF, secondary PAP related to hematologic malignancy, immune defects, inhalation or infection, and inherited mutations affecting surfactant production.

Histologically, in classic autoimmune PAP, there is patchy filling of alveolar spaces with granular or globular eosinophilic material (Fig. 8.6a, b) that is PAS positive and diastase resistant. Alveolar architecture is well preserved with thin alveolar walls and an absence of significant inflammatory cells, although foamy macrophages and cholesterol clefts may be present (Fig. 8.6b). Because transbronchial biopsies are small and may not necessarily sample the involved alveoli, bronchoalveolar lavage is more likely to detect the proteinaceous material.

Grossly the bronchoalveolar fluid in untreated PAP is milky or cloudy due to the abundant proteinaceous material. Classic cytologic findings in adult patients include large eosinophilic globules and few macrophages in a background of eosinophilic proteinaceous debris [37], though findings in treated patients may be more subtle and include many more foamy macrophages. As in tissue sections, the material is PAS positive and diastase resistant (Fig. 8.6c). While PAS-D stain can confirm the nature of the globules when present, it is not required to exclude pulmonary alveolar proteinosis since the material is also visible on routine stains such as H&E (Fig. 8.6d) and Pap (Fig. 8.6e). PAS-D positivity is not specific for surfactant material and can be seen with other types of proteinaceous debris. A combined PAS-alcian blue stain has been used to demonstrate that the material is alcian blue negative (mucous is positive by alcian blue), but this is not used in routine clinical practice. Similarly, electron microscopy has been used to demonstrate that the proteinaceous material contains surfactant material; however, this is time consuming and expensive and not widely available.

The presence of PAP-type globules are not entirely specific for surfactant-related disorders. Although not seen in normal patients, they can be present in smaller numbers in patients with other interstitial lung diseases [38, 39]. In these cases they are usually present in smaller quantities, but precise quantification is not possible.

Particularly in immunosuppressed patients, pulmonary alveolar proteinosis can be associated with infectious organisms, and silver stains such as GMS are typically performed to rule out infection in conjunction with culture results.

Histologic findings in patients with genetic surfactant deficiencies are more variable. While a subset of infants has a PAP pattern on histology, this is usually accompanied by an expanded alveolar interstitium and reactive pneumocytes. Other infants have a “desquamative” interstitial pneumonia pattern in which alveolar spaces are predominantly filled with macrophages, and still others (particularly older children) have much more subtle interstitial findings with rare foci of airspace material [40, 41]. Although large series specifically describing bronchoalveolar lavage fluid are not available, these patients would be expected to have less proteinaceous debris in the bronchoalveolar fluid, and when present, the eosinophilic material has usually been described as granular rather than globular. In some cases, foamy macrophage are more prominent. Given the wide range of histology, bronchoalveolar lavage therefore may be helpful but is not necessarily sensitive for establishing a diagnosis of surfactant abnormality in these disorders.

Special Stains for Organisms

Special stains for organisms can be performed on cytology specimens similar to paraffin-embedded tissue, but due to overlap with similar stains performed in the microbiology lab (gram and acid fast bacilli), generally only silver stain for fungus is performed as part of cytology examination. Silver stains such as Gomori methenamine silver (GMS) highlight the walls of yeasts and fungal

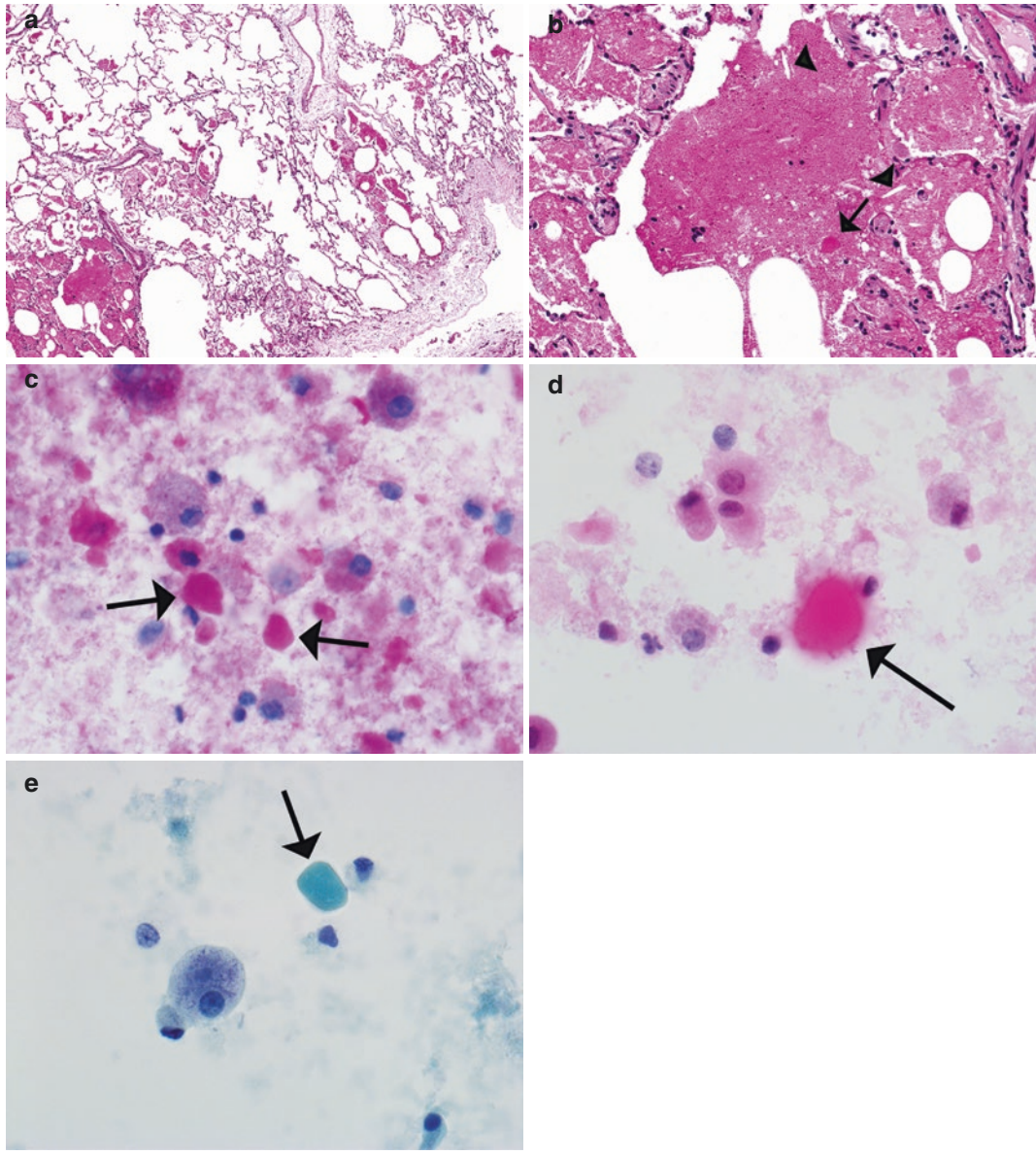

Fig. 8.6 (**a**) Low power view of the histology of pulmonary alveolar proteinosis with PAS-D stain shows patchy alveolar filling with dark pink material. (**b**) Higher power view shows that the material is granular with some solid globules (arrows) and cholesterol clefts (arrowhead). The alveolar septa are thin and lined by flattened epithelial cells. (**c**) PASD stain shows the globules (arrows) and granular debris are resistant to diastase. (**d**) H&E stain of cytology specimen shows finely granular eosinophilic (pink) material in the background and one globule (arrow). (**e**) With pap stain, the proteinaceous material may vary from blue green (arrow) to an orange tint

hyphae. Finding yeast or hyphael forms in bronchoalveolar lavage fluid does not distinguish between colonization of airways and invasive infection. Budding yeast, sometimes with pseudohyphae, may be seen as a feature of oral contamination when abundant bacteria and squamous cells are present.

As in tissue sections, identification of fungal forms or yeast is somewhat limited due to markedly overlapping morphologic characteris-

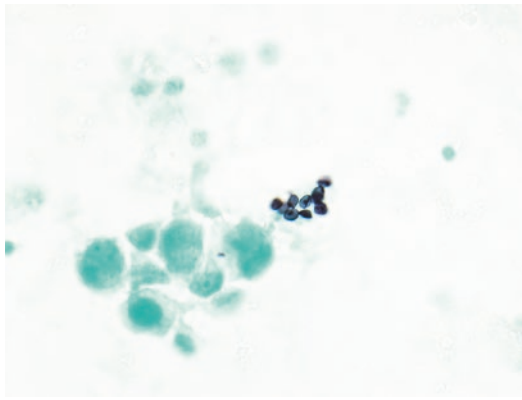

Fig. 8.7 In this silver stain, a cluster of pneumocystis organisms stain black. Some have a central dot while others are cup shaped. A green counterstain shows adjacent alveolar macrophages

tics – specific fungal features such as fruiting bodies are almost never present. In general, if sufficient hyphae are present they can be generally separated into narrow, septate, acute angle types (*Aspergillum*, *Fusarium* and others) and broad, pauci-septate types (*Mucorales*), but specific identification is best performed by culture or molecular techniques.

The cyst wall of pneumocystis is stained by GMS, which shows a small (approximately 4–6 μm) round cyst, often with either a central "dot" or a collapsed cup shape, depending on the orientation of the organism (Fig. 8.7). The trophozoite form of pneumocystis does not stain with GMS but can be identified on other common stains such as Giemsa.

References

1. Fan LL, Lung MC, Wagener JS. The diagnostic value of bronchoalveolar lavage in immunocompetent children with chronic diffuse pulmonary infiltrates. Pediatr Pulmonol. 1997;23(1):8–13.
2. Shell R, Nicol K. Pediatric bronchoalveolar lavage: practical considerations and future prospects. Pediatr Dev Pathol. 2010;13(4):255–64.
3. Heron M, Grutters JC, ten Dam-Molenkamp KM, Hijdra D, van Heugten-Roeling A, Claessen AM, et al. Bronchoalveolar lavage cell pattern from healthy human lung. Clin Exp Immunol. 2012;167(3):523–31.
4. Meyer KC, Soergel P. Variation of bronchoalveolar lymphocyte phenotypes with age in the physiologically normal human lung. Thorax. 1999;54(8):697–700.
5. Riedler J, Grigg J, Stone C, Tauro G, Robertson CF. Bronchoalveolar lavage cellularity in healthy children. Am J Respir Crit Care Med. 1995;152(1):163–8.
6. Ratjen F, Bredendiek M, Brendel M, Meltzer J, Costabel U. Differential cytology of bronchoalveolar lavage fluid in normal children. Eur Respir J. 1994;7(10):1865–70.
7. Midulla F, Villani A, Merolla R, Bjermer L, Sandstrom T, Ronchetti R. Bronchoalveolar lavage studies in children without parenchymal lung disease: cellular constituents and protein levels. Pediatr Pulmonol. 1995;20(2):112–8.
8. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med. 2012;185(9):1004–14.
9. Guidelines of the Papanicolaou Society of Cytopathology for the examination of cytologic specimens obtained from the respiratory tract. Papanicolaou Society of Cytopathology Task Force on Standards of Practice. Diagn Cytopathol. 1999;21(1):61–9.
10. Marguet C, Jouen-Boedes F, Dean TP, Warner JO. Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough, or cystic fibrosis. Am J Respir Crit Care Med. 1999;159(5 Pt 1):1533–40.
11. Choi SH, Hong SB, Hong HL, Kim SH, Huh JW, Sung H, et al. Usefulness of cellular analysis of bronchoalveolar lavage fluid for predicting the etiology of pneumonia in critically ill patients. PLoS One. 2014;9(5):e97346.
12. Meyer KC. The clinical utility of bronchoalveolar lavage in interstitial lung disease – is it really useful? Expert Rev Respir Med. 2014;8(2):133–5.
13. Giovannini-Chami L, Blanc S, Hadchouel A, Baruchel A, Boukari R, Dubus JC, et al. Eosinophilic pneumonias in children: a review of the epidemiology, diagnosis, and treatment. Pediatr Pulmonol. 2016;51(2):203–16.
14. Oermann CM, Panesar KS, Langston C, Larsen GL, Menendez AA, Schofield DE, et al. Pulmonary infiltrates with eosinophilia syndromes in children. J Pediatr. 2000;136(3):351–8.
15. Ratjen F, Costabel U, Griese M, Paul K. Bronchoalveolar lavage fluid findings in children with hypersensitivity pneumonitis. Eur Respir J. 2003;21(1):144–8.
16. Sherman JM, Winnie G, Thomassen MJ, Abdul-Karim FW, Boat TF. Time course of hemosiderin production and clearance by human pulmonary macrophages. Chest. 1984;86(3):409–11.
17. Epstein CE, Elidemir O, Colasurdo GN, Fan LL. Time course of hemosiderin production by alveolar macrophages in a murine model. Chest. 2001;120(6):2013–20.
18. De Lassence A, Fleury-Feith J, Escudier E, Beaune J, Bernaudin JF, Cordonnier C. Alveolar hemorrhage. Diagnostic criteria and results in 194 immu-

nocompromised hosts. Am J Respir Crit Care Med. 1995;151(1):157–63.
19. Salih ZN, Akhter A, Akhter J. Specificity and sensitivity of hemosiderin-laden macrophages in routine bronchoalveolar lavage in children. Arch Pathol Lab Med. 2006;130(11):1684–6.
20. Maldonado F, Parambil JG, Yi ES, Decker PA, Ryu JH. Haemosiderin-laden macrophages in the bronchoalveolar lavage fluid of patients with diffuse alveolar damage. Eur Respir J. 2009;33(6):1361–6.
21. Godeau B, Schaeffer A, Bachir D, Fleury-Feith J, Galacteros F, Verra F, et al. Bronchoalveolar lavage in adult sickle cell patients with acute chest syndrome: value for diagnostic assessment of fat embolism. Am J Respir Crit Care Med. 1996;153(5):1691–6.
22. Williams RA. Lipid-laden alveolar macrophages may indicate either aspiration pneumonia or sickle cell acute chest syndrome associated with pulmonary fat embolism. Arch Pathol Lab Med. 1995;119(9):772.
23. Layden JE, Ghinai I, Pray I, et al. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Final Report. N Engl J Med. 2020;382(10):903–16.
24. Maddock SD, Cirulis MM, Callahan SJ, et al. Pulmonary Lipid-Laden Macrophages and Vaping. N Engl J Med. 2019;381(15):1488–89.
25. Viswam D, Trotter S, Burge PS, Walters GI. Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. BMJ Case Rep. 2018;2018
26. Colombo JL, Hallberg TK. Recurrent aspiration in children: lipid-laden alveolar macrophage quantitation. Pediatr Pulmonol. 1987;3(2):86–9.
27. Moran JR, Block SM, Lyerly AD, Brooks LE, Dillard RG. Lipid-laden alveolar macrophage and lactose assay as markers of aspiration in neonates with lung disease. J Pediatr. 1988;112(4):643–5.
28. Ding Y, Simpson PM, Schellhase DE, Tryka AF, Ding L, Parham DM. Limited reliability of lipid-laden macrophage index restricts its use as a test for pulmonary aspiration: comparison with a simple semiquantitative assay. Pediatr Dev Pathol. 2002;5(6):551–8.
29. Kazachkov MY, Muhlebach MS, Livasy CA, Noah TL. Lipid-laden macrophage index and inflammation in bronchoalveolar lavage fluids in children. Eur Respir J. 2001;18(5):790–5.
30. Basset-Leobon C, Lacoste-Collin L, Aziza J, Bes JC, Jozan S, Courtade-Saidi M. Cut-off values and significance of oil red O-positive cells in bronchoalveolar lavage fluid. Cytopathology. 2010;21(4):245–50.
31. Collins KA, Geisinger KR, Wagner PH, Blackburn KS, Washburn LK, Block SM. The cytologic evaluation of lipid-laden alveolar macrophages as an indicator of aspiration pneumonia in young children. Arch Pathol Lab Med. 1995;119(3):229–31.
32. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. Pediatr Pulmonol. 1999;27(6):419–22.
33. Furuya ME, Moreno-Cordova V, Ramirez-Figueroa JL, Vargas MH, Ramon-Garcia G, Ramirez-San Juan DH. Cutoff value of lipid-laden alveolar macrophages for diagnosing aspiration in infants and children. Pediatr Pulmonol. 2007;42(5):452–7.
34. Rosen R, Fritz J, Nurko A, Simon D, Nurko S. Lipid-laden macrophage index is not an indicator of gastroesophageal reflux-related respiratory disease in children. Pediatrics. 2008;121(4):e879–84.
35. Langston C, Pappin A. Lipid-laden alveolar macrophages as an indicator of aspiration pneumonia. Arch Pathol Lab Med. 1996;120(4):326–7.
36. Reid-Nicholson M, Kulkarni R, Adeagbo B, Looney S, Crosby J. Interobserver and intraobserver variability in the calculation of the lipid-laden macrophage index: implications for its use in the evaluation of aspiration in children. Diagn Cytopathol. 2010;38(12):861–5.
37. Martin RJ, Coalson JJ, Rogers RM, Horton FO, Manous LE. Pulmonary alveolar proteinosis: the diagnosis by segmental lavage. Am Rev Respir Dis. 1980;121(5):819–25.
38. Chou CW, Lin FC, Tung SM, Liou RD, Chang SC. Diagnosis of pulmonary alveolar proteinosis: usefulness of papanicolaou-stained smears of bronchoalveolar lavage fluid. Arch Intern Med. 2001;161(4):562–6.
39. Maygarden SJ, Iacocca MV, Funkhouser WK, Novotny DB. Pulmonary alveolar proteinosis: a spectrum of cytologic, histochemical, and ultrastructural findings in bronchoalveolar lavage fluid. Diagn Cytopathol. 2001;24(6):389–95.
40. Griese M. Pulmonary alveolar proteinosis: a comprehensive clinical perspective. Pediatrics. 2017;140(2)
41. Thouvenin G, Abou Taam R, Flamein F, Guillot L, Le Bourgeois M, Reix P, et al. Characteristics of disorders associated with genetic mutations of surfactant protein C. Arch Dis Child. 2010;95(6):449–54.

9 Bronchoalveolar Lavage: Microbial Evaluation

Bacteriology, Virology, Parasitology, Mycology, and Airway Microbiome

Kevin J. Downes, Jennifer M. Bouso, and Paul J. Planet

Introduction: Overall Diagnosis of Infection by Bronchoscopic Techniques

Flexible bronchoscopy with bronchoalveolar lavage (BAL) or intraluminal (transbronchial) biopsy can be an invaluable tool in diagnosing pulmonary infectious disease, and in many cases, it may guide treatment. Bronchoscopy allows for both visualization of airway and mucosal surfaces and sampling that can reveal local inflammatory, immunological, or pathogenic processes.

Direct visualization may reveal signs of infection (mucus production, erythema, and edema) in the trachea, mainstem bronchi, and subsegmental bronchi. While more distal airways are more difficult to visualize, especially in smaller children and infants, mucus plugging may direct the bronchoscopist to particular lobes that appear to harbor infection. Even with localized disease, mucus and edema may be present throughout the larger airways due to local immune responses and a functional mucociliary elevator.

Local sampling can be accomplished through BAL or biopsy. The retrieved specimens can then be subjected to standard techniques in microbial culture, cytology, histopathology, along with other molecular tests. Because of higher rates of adverse complications in biopsy, BAL is generally preferred as the initial diagnostic tool [1–5], but biopsy may be necessary in cases where the infection is mostly intraparenchymal, and it may have a higher diagnostic yield [5, 6]. Standard culture techniques still represent the gold standard for identifying potential pathogens, but it should be noted that overall diagnostic yield is limited with many studies reporting rates of less than 50% [7, 8]. Multiple new molecular and culture-independent approaches are being developed, which may improve this yield.

While bronchoscopy is generally considered to be a safe procedure, risks and benefits of the procedure should always be weighed, particularly in the unstable or immunocompromised patient [2, 9–11]. Bronchoscopic evaluation with sampling by either BAL or biopsy may be considered in the following specific situations: (1) critically ill patients who warrant bronchoscopy for broad microbiologic testing and rapid diagnosis; (2)

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_9

high-risk patients (i.e., CF, immunocompromised state, history of lung transplant, and concern for or diagnosis of interstitial lung disease) with radiographic findings consistent with an infectious etiology; (3) any child with high clinical suspicion for mycobacterial or fungal disease and who is unable to expectorate sputum; and (4) children who have failed to respond, worsened, or relapsed after empiric therapy. Young children are often not able to produce sputum or cough forcefully enough to expectorate, and bronchoscopy may represent the only way to obtain diagnostic samples from the lower respiratory tract, although induced sputum can be attempted following hypertonic saline nebulization to assist with mucus production.

The nonspecific findings (e.g., nodules, tree-in-bud, or ground-glass opacities) seen on chest imaging prior to bronchoscopy often constitute the major motivation for pursuing an infectious workup with bronchoscopy, and the imaging can often help direct the bronchoscopist to a lobe of particular disease. However, imaging is not an absolute prerequisite to bronchoscopy, and in cases where imaging is not available or in cases of diffuse disease, bronchoalveolar lavage may have a higher yield in the right middle lobe and/or lingula.

The ultimate goal of bronchoscopy in the infectious disease context is to garner information that will lead to changes or refinements in therapy. Table 9.1 displays an approach to the diagnostic evaluation for infection using bronchoscopy. Despite low definitive diagnostic yields, several studies have shown that bronchoscopy has an impact on treatment decisions [5, 8, 12, 13]. In addition to identifying a pathogen that can be specifically targeted over a defined duration, the results of bronchoscopy, even if they are not completely definitive, can help simplify the antimicrobial regimen, limiting unnecessary exposure to antibiotics and all of the attendant risks such as organ toxicities, allergic reactions, microbial dysbiosis, and the fostering of antibiotic resistance.

This chapter discusses the diagnosis of infections using bronchoscopy with an emphasis on microbiology. We also discuss relevant histopathologic, immunologic, molecular, and culture-independent diagnostic techniques.

Bacteriology

Bacterial Etiologies and Sampling

The most common bacterial causes of lower respiratory tract infection (LRTI) are familiar respiratory pathogens that cause community-associated pneumonia (CAP), such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. However, the relative importance of each of these organisms is difficult to determine because most disease is treated empirically and most infections go uncultured because the site of infection is difficult to access. *Staphylococcus aureus* is an unusual cause of CAP (approximately 1% overall), but the severity of infection is high, with patients frequently requiring mechanical ventilation and often presenting with parapneumonic effusion [14–16]. Therefore, *S. aureus* should always be considered in serious cases of pneumonia. In addition, over the past 15 years, there has been heightened concern in the United States, based on increased rates of *S. aureus* CAP associated with the community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) epidemic lineage USA300 [14], that anti-MRSA treatment may need to be considered in severe pneumonia.

Bronchoscopy with BAL or biopsy for culture is rarely performed in uncomplicated CAP, but it presents a diagnostic option for more complicated bacterial pneumonia or pneumonia that fails to respond to empiric antibiotic treatment. De Shutter et al reported high rates of nontypeable *Haemophilus influenzae* (NTHi) in BAL cultures from patients with nonresponding or recurrent CAP [17]. This study also identified *M. catarrhalis* and *S. pneumoniae* as common pathogens. Tsai et al (2017) reported "viridans" group streptococci, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* as the most common pathogens in BALs from patients with nonresponding CAP. Rates of detection of a pathogen

Table 9.1 Recommended testing for bronchoscopic-based sampling in cases when infection is clinically suspected

	Cytology	Bacteria	Viruses	Fungi	Mycobacteria	Other
Routine testing (all patients)	Quantitative cell count Microscopy Consider: Oil red-O stain (for lipid-laden macrophages) Iron stain (for hemosiderin-laden macrophages) Periodic Acid-Schiff (PAS) stain	Stains: Gram stain Culture: Quantitative aerobic respiratory culture	Molecular tests: PCR-based basic viral panel (if testing not performed on NP specimen)	Stains: Grocott-Gomori methenamine silver (GMS) stain Periodic acid Schiff (PAS) stain Calcofluor white KOH Culture: Fungal culture	Stains: AFB Culture: Liquid and solid AFB culture	Consider: Mycoplasma PCR
Additional testing to be considered in immune-compromised individuals	Microscopy for parasites and fungi (particularly important when geographic exposures suggest specific infections not amenable to other testing) Pathology of biopsied samples		Pathogen-specific PCRs: EBV (in solid organ or hematopoietic cell transplant patient) CMV (in solid organ or hematopoietic cell transplant patient) VZV (when disseminated disease is suspected) HHV-6 (hematopoietic cell transplant or severe immune compromise; clinical relevance often difficult to interpret) HSV (in disseminated disease; clinical relevance may be difficult to interpret given prevalence of shedding from oral mucosa)	Molecular tests: *Pneumocystis jirovecii* PCR Other tests: *Aspergillus* galactomannan *Histoplasma* antigen (if exposure in endemic region) *Cryptococcus* antigen (rare cases)	Consider: Xpert/RIF® for TB	Consider: *Toxoplasma gondii* PCR (solid organ transplant recipients, particularly heart transplant) Legionella DFA

in nonresponding or recurring CAP have been reported to be as high as 76% when the lower respiratory tract is sampled [17].

Other diagnostic sampling techniques for LRTI have even poorer yields. When blood cultures are done in the setting of LRTI, they are positive in less than 3% of cases [18–21], although some studies have reported rates as high as 7% [22] or 11% [23] in community-acquired pneumonia (CAP). It is important to note that severity of pneumonia is positively associated with the likelihood of obtaining a positive blood culture with rates of 13–26% in the setting of an empyema or parapneumonic effusion [18, 24–27]. Sputum cultures can be difficult to obtain in younger children who cannot expectorate and may be reflective of commensal colonization with potential pathogens rather than the etiology of a LRTI [28]. Thoracentesis and transthoracic needle aspiration may have higher culture yields, but they are also significantly more invasive and are uncommon especially in less severe disease [28].

The so-called "atypical" causes of LRTI such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are more common in children >5 years [29–31]. These bacteria can be detected in BAL fluid [32, 33], but swabs of the upper respiratory tract (nasopharyngeal, oropharyngeal) as well as throat and nasal washes are often used to rule out LRTI [28]. If children can produce sputum, it may be the preferred sample for diagnosis of these organisms [28].

Legionella pneumophila is also a cause of LRTI that has been associated with infections both in hospitals and in the community [34]. *L. pneumophila* can be detected from BAL fluid using culture, which requires specific media (BYCE) and can take 3–5 days to grow, or by polymerase chain reaction (PCR)-based techniques, which produce results much more quickly but with less sensitivity [35, 36]. In practice, most disease is diagnosed by the urine antigen test, a monoclonal antibody test that specifically targets *L. pneumophila* serogroup 1. Because serogroup 1 causes anywhere from 50% to 80% of Legionnaire's disease, it is possible that cases are missed when this single modality is used [35].

Staphylococcus aureus, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* are the most prevalent causes of LRTI in ventilator-associated pneumonia (VAP); other common causes include gram-negative pathogens such as *Klebsiella* spp., *Enterobacter* spp., *Escherichia coli*, *Serratia* spp., and occasionally *Acinetobacter* spp. [37–39]. The role of anaerobic bacteria in VAP is not well understood, but it is likely that there are high levels of exposure and possibly colonization with commensal anaerobes during intubation and ventilation [40]. The gold standard for diagnosis of VAP is direct observation of the infected tissue and culture, and thus requires bronchoscopy [41]. However, the diagnosis is often made through clinical and radiographic findings because of the risks associated with more invasive procedures [42, 43]. Comparison between different methods for obtaining cultures in VAP, including BAL, nonbronchoscopic (NB) BAL, transbronchial biopsy, tracheal aspiration (TA), protected specimen brush, and postmortem autopsy, has shown enormous heterogeneity and incongruence [37, 42–53]. BAL is a generally accepted reference sampling method, but in clinical practice, TA is more often performed because of feasibility and safety [48, 54, 55]. However, TA is likely to be contaminated with upper respiratory microbiota or may simply represent colonization of the endotracheal tube, and therefore, it has low specificity [49, 52, 56].

Common bacterial causes of LRTI in immunocompromised hosts encompass both the common causes of CAP (e.g., *S. pneumoniae* and *H. influenzae*) and more opportunistic pathogens associated with VAP (*P. aeruginosa* and *S. aureus*) [57, 58]. Despite the appropriate emphasis on diagnosis of fungi and some viruses in these patients, potentially pathogenic bacteria are identified in about a third of positive BAL samples [8, 57]. It is, however, important to reiterate that overall yields in immunocompromised pediatric patients vary widely from 28% to 68% [8].

Bronchoscopy with BAL is often used in cystic fibrosis (CF) to determine the presence of LRTI with common bacterial CF pathogens such as *P. aeruginosa*, *S. aureus*, *H. influenzae*,

Stenotrophomonas maltophilia, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex as well as nontuberculous mycobacteria (NTM) and fungi, which will be discussed below. Anaerobic bacteria such as *Prevotella* spp. have recently been appreciated to be important microorganisms in CF, though their role as pathogens is not firmly established [59–61]. In CF, the prevalence of pathogens is linked to the age of the patient, with *S. aureus* and *H. influenzae* being more prevalent in young children, and gram negatives such as *P. aeruginosa* becoming dominant in the adolescent years [62]. In addition, the distribution of pathogens throughout the lung can be variable with both phenotypic variation within a species [63–66] (e.g., antibiotic resistance, metabolic status, and mucoidy), as well as species composition [67–69] (e.g., relative abundance, presence/absence). Noninvasive upper respiratory tract sampling (oropharyngeal, nasopharyngeal, and cough swabs) and expectorated sputum are commonly used for surveillance of pathogens in CF, and studies have reported conflicting negative and positive predictive values for LRTI compared to BAL [70–77]. One study showed that in adults, BAL and protected brushing samples were not superior to sputum samples in *P. aeruginosa* yield and may have given a more representative picture of the entire infecting population [78]. Other studies showed no clinical or cost benefit, and higher rates of adverse events with treatment based on BAL culture (reviewed in [79]). BAL may be especially useful in children who cannot expectorate [70, 80, 81], but induced sputum (using hypertonic saline) is an emerging alternative that appears to be safe and has potentially higher microbiological yields than other noninvasive sampling techniques [82–86]. Indeed, some studies have shown that induced sputum may have the same or better microbiological yield than BAL [87–90]. Although there is considerable doubt about the overall utility of BAL in CF microbiological diagnosis, it remains the gold standard for pathogen detection at the site of infection, and may be useful on a case-by-case basis, or if there are unexplained clinical changes without changes in surveillance microbiology.

Methods for Detecting Bacterial Infection in Bronchoscopic Samples

Culture

After gram staining for standard bacterial pathogens, which can give an initial diagnostic indication of the possible, but clearly not definitive, disease etiology [91], BAL fluid is subjected to standard bacterial cultures. While there is heterogeneity in clinical laboratory practice, most laboratories use an array of different culture media (e.g., blood, chocolate, and MacConkey and colistin–nalidixic acid agars) with additional media used for specific diseases (e.g., *B. cepacia* media used in CF cultures). While certain organisms may be reported by laboratories at any abundance (e.g., MRSA, *Nocardia* spp., *P. aeruginosa*), quantitative culture techniques have been shown to enhance the interpretation of BAL culture [28, 92–95]. A cutoff of $>10^3$ colony forming units (CFUs) has been shown to be significant with sensitivity of 90% and specificity of 97% [28, 96], but many studies and laboratories use $>10^4$ CFUs, which yield specificities as high as 100% [94, 97, 98]. The standard respiratory pathogens such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* as well as common bacterial VAP and CF pathogens have relatively high yields with standard culture, though published yields vary greatly [28]. *M. pneumoniae* and *C. pneumoniae* are rarely cultured in clinical practice because of their fastidious growth requirements. As noted above, culture may be helpful for detection of *Legionella pneumophila*, but this requires special culture techniques and a longer culture time [35]. It is also worthwhile noting that samples are rarely grown anaerobically, and therefore will not detect obligate anaerobes.

One important limitation of culture is that it relies on the retrieval of living bacteria. Indeed, prior exposure to antibiotics has been shown to affect accuracy and yields [7, 45, 99–101]. One study reported that yields were 63% when the BAL was done within 3 days of starting treatment, whereas this dropped to 58% between 3

and 14 days after starting treatment and 34% after 14 days of treatment [7].

PCR/Nucleic Acids

Culture remains the primary diagnostic modality for most bacterial causes of LRTI, but PCR-based techniques may increase yield especially after the initiation of antibiotics [102]. Targeted PCR-based techniques are available for *S. pneumoniae* [103–108], and these tests are easiest to interpret when used on pleural fluid samples, for which one study showed to have 78% sensitivity and 93% specificity [103]. Directed PCR-based strategies have been developed for *H. influenzae*, *S. aureus,* and *M. catarrhalis* as well [109–112]. Only a few studies address targeted PCR for respiratory pathogens in BAL [113, 114], but new multiplex PCR systems may offer high sensitivity and specificity [115]. The diagnostic utility of PCR for *S. pneumoniae* in other samples such as sputum and throat swabs is unclear, and they are plagued by the problem of differentiating between colonization and infection [112, 116–119], a problem that might be partially remedied by considering absolute bacterial burden [107, 120–122]. Conflicting results have been seen with PCR for *S. pneumoniae* blood and serum samples [116, 120, 123–126]. The test for *S. pneumoniae* urine antigen may be a more sensitive and cost effective [127]. Broad range 16S rRNA amplicon approaches that can detect multiple pathogens form pleural fluid have only marginally better yields compared to culture [128].

PCR and nucleic acid techniques are favored for detection of *M. pneumoniae* and *C. pneumoniae*, and they are often included in PCR respiratory viral panels. As noted above, these are often obtained from upper respiratory tract samples of the nasopharynx or oropharynx. However, the available data suggest that yields may be better from sputum [28] probably due to the overall abundance of the organism in the sample. There are only very limited available data on the yields from BAL specimens. PCR-based tests are commercially available for detection of *L. pneumophila*, but they have limited sensitivity [35].

Mycobacteriology

Mycobacteria are gram-positive, aerobic, acid-fast bacilli that cause significant disease worldwide, primarily affecting vulnerable populations [129–133]. Categorization of these organisms is classically defined by the Runyon classification, which relies on observation of phenotypic traits (growth rate and photochromogenicity) [134]. Further, mycobacteria may be defined by their parasitism (facultative versus obligate) and ecologic predilection (saprophytic, zoonotic, and human pathogens). For clinical purposes, these organisms are most deductively classified by the disease as they manifest in humans: *Mycobacterium tuberculosis* complex (i.e., *M. tuberculosis*, *M. bovis*, *M. africanum*) causing pulmonary or extrapulmonary tuberculosis; *Mycobacterium leprae* causing leprosy; and nontuberculosis mycobacteria (NTM) causing pulmonary, disseminated, and soft-tissue infections. In this subsection, we focus on pulmonary manifestations of tuberculous and nontuberculous disease with regard to diagnostic challenges, the role of bronchoscopy, and available microbiologic diagnostic techniques.

Tuberculosis

As the oldest documented human pathogen, tuberculosis (TB) remains the leading cause of death by an infectious agent worldwide with an estimated 1.7 billion people infected and nearly two million deaths per year [135]. Multidrug resistant TB (MDR-TB) harboring resistance to two of the first-line antimicrobial agents (isoniazid and rifampin) affects over 500,000 new patients per year [135]. The World Health Organization and United Nations have developed Sustainable Development Goals (SDGs) as part of the End TB Strategy by 2035, which is threatened mostly by increasing drug resistance and sociopolitical challenges [135]. Despite these global initiatives, socioeconomic factors (e.g., extreme poverty, overcrowding, malnutrition, and living in a developing country) are still the major determinants of clinical outcomes [136].

TB does not have an environmental or zoonotic reservoir and is instead transmitted from person-to-person by the inhalation of droplet nuclei (1–5 μm) filled with acid-fast bacilli that have been expelled into the air by a patient with active TB. While exposure does not imply infection, over 95% of infected individuals will advance to latent TB infection (LTBI), a state of clinical quiescence and slow bacterial replication held at bay by an intact adaptive immune system. Progressive primary tuberculosis is rare and occurs in patients with deficiencies in adaptive immunity, young children, and the elderly. However, most infections in children and adolescents are asymptomatic. Reactivated TB, prompted by the development of a risk factor (e.g., solid organ transplant, immunosuppression, HIV/AIDS), classically presents with productive cough, fever, weight loss, growth delay, chills, and night sweats. Active pulmonary TB in adults is distinguished by cavitary lung disease with caseous, necrotizing granulomas favoring the upper lobes. However, children rarely have cavitary disease, but rather present with nonspecific radiographic findings (atelectasis, pleural infiltration or effusion, mediastinal lymphadenopathy, lower lung abnormalities, or a military pattern). Congenital TB presents with a sepsis-like picture, bronchopneumonia, and hepatosplenomegaly. In all ages, TB disease can span the entire airway, including laryngeal, tracheal, and endobronchial involvement [137, 138].

Diagnosis of active pulmonary TB requires positive delayed-type hypersensitivity (DTH) reaction by positive tuberculin skin test (TST) with respiratory symptoms and radiographic evidence of disease. In the absence active TB, LTBI is diagnosed by positive TST or interferon-γ (INF-γ) assay (IGRA). Traditionally, diagnosis of active disease is confirmed by three positive acid-fast bacilli (AFB) cultures at least 8 hours apart [138]. Childhood tuberculosis can be challenging diagnostically because of their inability to produce sufficient sputum and the wide range of possible radiographic findings and presentations. The Red Book currently recommends all children with suspicion for TB who cannot produce sputum to have three consecutive early morning gastric aspirates for AFB smear and culture [138]. While not established as the first line of specimen collection in children, obtaining a radiographic-directed BAL sample for smear and culture can be extremely useful diagnostically. Furthermore, as TB affects the larger airways in children with rates of 41–63%, endobronchial disease can be directly observed, classified, and sampled via bronchoscopy [139]. In addition, endobronchial disease can result in severe airway obstruction or strictures that require bronchoscopic intervention (Fig. 9.1).

Treatment should be guided by antimicrobial susceptibility testing and directed by an infectious disease specialist.

Nontuberculous Mycobacteria

NTMs are present ubiquitously in the environment, living in biofilms in water and soil, and cause opportunistic disease in at-risk populations [140–145]. Immunocompromised hosts, the elderly, patients with cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), interstitial lung disease, and non-CF bronchiectasis are at increased risk due to decreased mucociliary clearance, inflamed or bronchiectatic airways, and structural lung damage. Susceptibility is also increased in patients with immune deficiencies affecting INF-γ, interlukin-12 (IL-12), and tumor necrosis factor-alpha (TNF-α) signaling pathways, as in the case of HIV infection or treatment with a TNF-α inhibitor [146]. Patients with pulmonary alveolar proteinosis (PAP) are at higher risk for NTM infection, as well [146].

In the United States, the largest studies estimate prevalence in the general population at about 5.3 per 100,000 persons with highest rates in elderly over 80 years old and those living in southeastern states and in Hawaii [129, 130, 132, 147, 148]. Increases in prevalence are estimated to be rising at rates of 2.6–11.8% per year [130–132, 148, 149]. A global collaboration headed by the NTM-Network European Trials Group (NTM-NET) reviewed over 20,000 patient samples from 30 countries and 6 continents and identified *Mycobacterium avium* complex (MAC) as

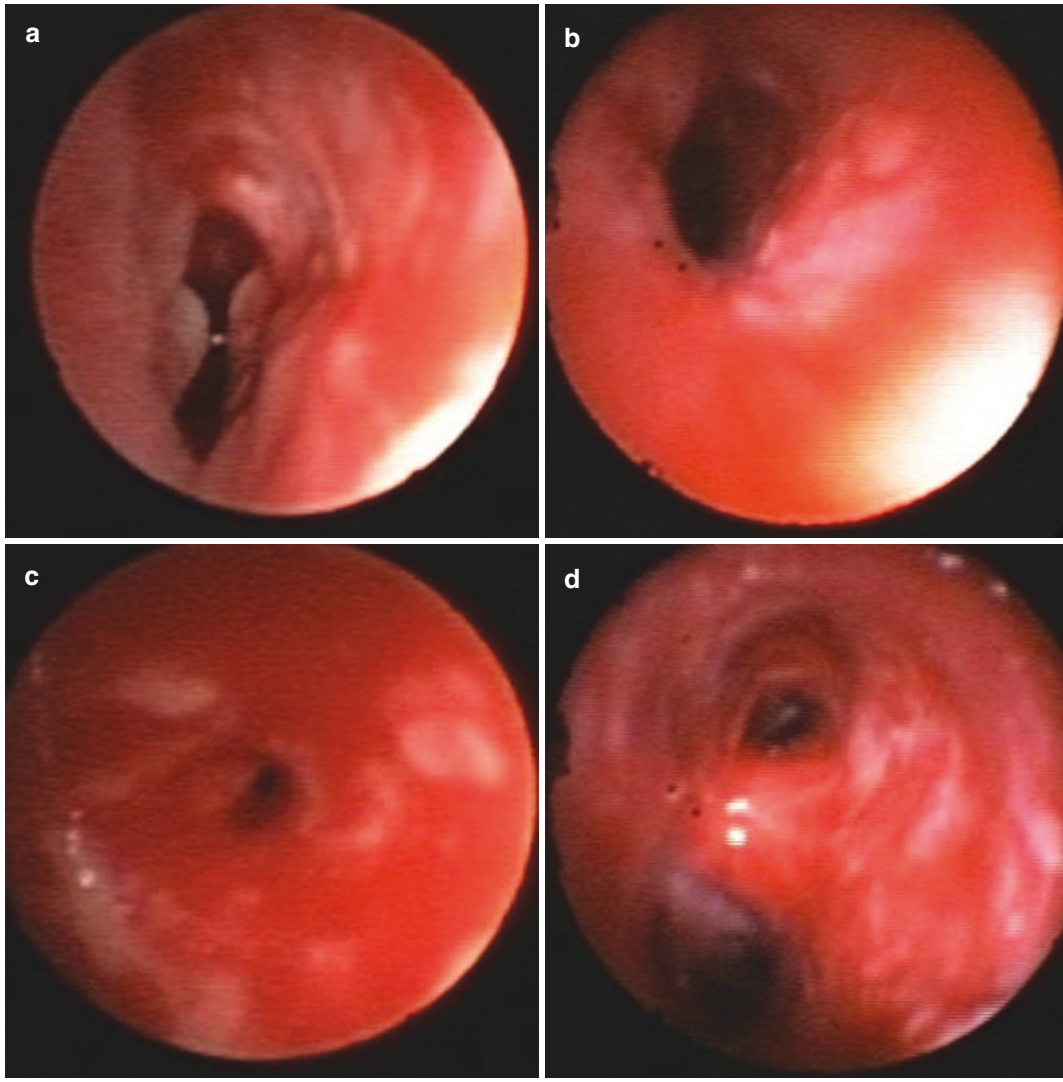

Fig. 9.1 Endobronchial TB causing stenosis of the left mainstem bronchus (**a**) and left upper lobe bronchus (**b**) in a 12-year-old boy with active TB. Postballoon dilation, narrowing is improved in (**c**) and (**d**), respectively

the predominant species complex worldwide at 47%, followed by *M. gordonae* (11%), *M. xenopi* (8%), *M. fortuitum* complex (7%), *M. kansasii* (4%), and *M. abscessus* (3%) [150]. *M. gordonae*, *M. terrae*, and *M. fortuitum* complex are often environmental contaminants and are unlikely to cause disease [151, 152]. The major causes of pulmonary disease in humans include MAC, *Mycobacterium abscessus* complex (MABSC), and *Mycobacterium kansasii* [130, 143, 146, 153–157].

Transmission typically occurs due to environmental exposure by inhalation route of aerosolized mycobacteria. Clinical manifestations of pulmonary NTM infection range from silent, chronic colonization to severe, progressive lung disease. The American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) 2007 diagnostic criteria require pulmonary symptoms, specific radiographic findings (nodular or cavitary opacities or multifocal bronchiectasis) with exclusion of other diagnoses, and

microbiologic evidence of disease by either: two positive AFB cultures or one positive culture from bronchial washing, bronchoalveolar lavage (BAL), transbronchial biopsy (TBB), or endobronchial ultrasound-guided (EBUS) biopsy with histopathologic features consistent with mycobacterial disease [151].

In the CF population, average NTM prevalence in the United States has climbed from 1.3% in 1984 to an average of 14% in 2014, with some states as high as 28% [129, 147, 154, 157–159]. Possible causes for the rise of recognized NTM disease in CF are manyfold and include longer patient life-expectancy, development of NTM-adapted niches due to use of broad-spectrum antibiotic usage, and increased awareness and testing as per the 2013 Cystic Fibrosis Foundation (CFF) update on infection prevention and control guidelines [160]. Risk factors for NTM disease in CF are widely debated. The largest cross-sectional studies of CF patients to date suggest associations between NTM disease and better lung function, higher rates of coinfection with *Staphylococcus aureus* and lower rates of coinfection with *Pseudomonas aeruginosa*, a history of allergic bronchopulmonary aspergillosis (ABPA) or coinfection with *Aspergillus fumigatus*, and the chronic use of azithromycin or systemic steroids. However, smaller, less robust studies have not successfully replicated all of these associations and in some cases have demonstrated contradictory results [156, 157, 161–167]. Universally in CF, increased age is the most predictive risk factor for acquisition of NTM infection, which is likely secondary to repeated and prolonged exposure to the pathogen as well as host factors [140, 145, 166, 167]. Environmental studies have shown increased prevalence of NTM in areas associated with higher levels of atmospheric water and closer living proximity to water, although these associations tend to be region-specific [129, 156, 157, 162, 164–166, 168–178]. Widely debated is the potential for human transmissibility, which has been reported in the literature [176, 179] and is generally accepted to be a possible albeit rare modality for transmission.

Diagnosis of NTM in CF is problematic because (1) lung disease caused by mycobacterial infection resembles findings of the chronic progression of severe CF lung disease (tree-in-bud nodularity, bronchiectasis, and cavitation), and (2) NTM disease manifestations range from silent, chronic colonization to severe, progressive lung disease [161, 166, 167, 180–182]. In 2016, the Cystic Fibrosis Foundation (CFF) and European Cystic Fibrosis Society (ECFS) published a statement to assist clinicians with NTM diagnosis and treatment in CF [183]. The guidelines agree with the ATS/IDSA statement and additionally recommend chest high-resolution computed tomography (HRCT) to characterize disease and guide BAL sampling when indicated. When diagnostic criteria are met and clinical decline is appreciated despite standard CF care, treatment should be pursued and managed by an infectious disease specialist.

Similar to TB, antimicrobial regimens for NTM should be guided by susceptibility testing. Initial therapies for susceptible MAC pulmonary infection include a macrolide (clarithromycin or azithromycin), ethambutol, and either rifampin or rifabutin. Severe or cavitary MAC disease may warrant initiation with an IV aminoglycoside (amikacin or streptomycin). Typically, susceptible MABSC requires a more aggressive approach including initiation with IV amikacin, IV cefoxitin, IV imipenem or meropenem, and clarithromycin. For both complexes, other antimicrobial agents (fluoroquinolones, doxycycline or minocycline, linezolid, clofazimine, cycloserine, ethionamide, and capreomycin) or novel therapies (inhaled GM-CSF) are sometimes necessary [184]. Despite susceptibility-guided, multidrug regimens, NTM often acquires antibiotic resistance and is unable to be eradicated [151, 155, 159, 183, 185, 186]

Methods for Detecting Mycobacterial Infection in Bronchoscopic Samples

Many children are not able to produce sputum at a sufficient quantity for mycobacterial microbiologic testing, thus bronchoscopy with bronchoalveolar lavage can be an indispensable component in the

diagnosis of mycobacterial disease. In the critically ill patient, bronchoscopy for BAL, transbronchial biopsy (TBB), or endobronchial ultrasound-guided (EBUS) biopsy may be the only way to identify the etiology of pulmonary infiltrates or endobronchial disease. Furthermore, patients with cystic fibrosis and suspicion for NTM disease who are smear negative by sputum should undergo HRCT-guided bronchoscopic sampling as recommended by the CFF/ECFS [183].

Culture

The "gold standard" for diagnosis of mycobacterial infection is the AFB culture. The ATS/IDSA and CFF/ECFS recommend that both solid (Lowenstein–Jenson or Middlebrook 7H11) and liquid culture (Middlebrook 7H9) techniques be performed following standard decontamination measures (0.5% N-acetyl L-cysteine, 2% NaOH). Due to increased sensitivity and more rapid detection, liquid culture is recommended to be performed by the BD BACTEC™ MGIT™ Automated Mycobacterial Detection System which utilizes Middlebrook 7H9 liquid broth supplemented with 0.2% glycerol, 10% OADC (Oleic Albumin Dextrose Catalase), and PANTA antibiotic mixture (polymyxin B, amphotericin B, nalidixic acid, trimethoprim, azlocillin). Growth in liquid culture is faster than solid culture, and thus, positivity may be revealed sooner. For the clinician to be comfortable with negative results, both liquid and solid cultures must be finalized, with solid cultures requiring up to 8–12 weeks for appreciable growth to occur.

Molecular-Based Testing

All mycobacteria isolated by culture should be identified to the species level, primarily to distinguish between TB and NTM disease and secondarily because species classification dictates both treatment and anticipated outcomes [152, 187]. Current molecular techniques include nucleic acid amplification tests (NAAT) such as polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis, real-time PCR (RT-PCR), and line probe assays (LPA), chemiluminescent DNA probes, DNA sequencing, and matrix-assisted laser desorption ionization-time of flight spectrometry (MALDI-TOF) [138, 152, 188, 189]. Mycobacterial gene targets for NAAT include *rpoB* [190, 191], *hsp65* [192, 193], 16S rRNA genes [194–196], the 16S–23S gene spacer [197, 198], and *groES* [199]. Many clinical microbiology laboratories utilize MALDI-TOF for species identification due to its ability to speciate mycobacteria (63.8–98.6%) at a low cost [200–204]. Despite the advent of new technologies, few of the above modalities are able to classify organisms to the subspecies level, as is possible with whole-genome sequencing (WGS). As sequencing costs continue to decline, WGS will likely be utilized more in basic clinical diagnosis of mycobacterial infection.

For suspicion of TB disease, rapid NAATs can be useful for culture-independent diagnosis, though a negative test does not exclude disease and cannot replace standard culture. The first molecular test endorsed by the World Health Organization (WHO) in 2010 was the Xpert® MTB/RIF (Cepheid, USA), an assay that employs RT-PCR of the *rpoB* gene [135, 190]. By a large review (Cochrane review with expansion per the WHO 2013 Updated Report), the Xpert® MTB/RIF assay had a pooled sensitivity of 88% and pooled specificity of 99% for all specimens tested (expectorated and induced sputum, BAL, tissue samples, gastric aspirates, nasopharyngeal aspirates, and extrapulmonary samples) [205]. In children, sensitivities were 55–90%, 40–100%, and 40–100% for expectorated sputum, induced sputum, and gastric lavage, respectively, with specificities for all sites between 93% and 100%. One study has evaluated the efficacy of this test on BAL fluid in children with suspected TB and found 53% sensitivity and 100% specificity [206].

Pathology/Cytology

Staining and direct microscopy should always accompany AFB culture. The current recommendation for AFB staining is the fluorochrome tech-

nique, though Ziehl–Neelsen (ZN) and auramine–rhodamine (AR) staining methods may also be employed [151]. In the case of *M. tuberculosis*, and as is generalized to NTM pulmonary disease, smear positivity is associated with increased infectivity, higher bacterial loads, and worse disease burden. However, AFB smears can be negative in close to 50% of culture-positive patients [207]. During active TB infection, BAL cell counts will reveal a lymphocytic alveolitis with "foamy" (AFB-laden) macrophages and may have high percentages of immature macrophages (monocytes) thought to influx from the blood [137]. Biopsy specimens taken during bronchoscopy or by wedge resection will show granulomatous inflammation and should also be directly stained to identify AFB [146].

Virology

Introduction

Viruses are the most frequent cause of upper and lower respiratory tract infections in pediatric patients [208]. The challenges in diagnosing viruses as the cause of pneumonia are several-fold: (a) some viruses demonstrate prolonged shedding from the oropharynx or upper respiratory tract and detection in the upper respiratory tract may not reflect active lower respiratory tract infection [209, 210], (b) culture- and molecular-based detection methods do not distinguish infection from shedding or colonization [211], and (c) bacterial–viral and viral–viral coinfections are common [208]. Bronchoscopic approaches may help clinicians identify viral pathogens but do not necessarily solve the issue of distinguishing infection from shedding.

Respiratory Viruses

Several viruses fall into a group commonly referred to as "respiratory viruses." These viruses are from different families and have varying pathogenicity, but all have a predilection for causing respiratory tract infections. The most common viruses in this group are respiratory syncytial virus (RSV), influenza A and B, parainfluenza 1–3, human metapneumovirus (hMPV), adenovirus, human coronavirus (HCoV), and rhinovirus [208, 212], although numerous other viruses have been associated with pneumonia in children. Respiratory viruses are all more common in younger children [208, 213–215], likely due to a combination of social factors/exposures and immune naivety to these pathogens. Viral respiratory tract infections are typically self-limited, but can be life threatening in infants [216], immunocompromised children [217, 218], and children with underlying medical conditions such as asthma, heart disease, or cystic fibrosis [219].

The frequency of viral–bacterial and viral–viral coinfections makes estimation of the incidence of viral LRTIs due to specific pathogens challenging. In a recent study of 2219 children hospitalized with community-acquired pneumonia (CAP) at one of three US hospitals, viruses were detected in two-thirds [208]. Coinfections were present in 26% of all children with CAP, including 19% that had multiple viruses detected [208]. Thus, while studies report the incidence of detection of respiratory viruses in children with pneumonia, the proportion of pediatric pneumonia specifically caused by each organism is not known.

Viral pneumonia from respiratory viruses almost always develops as a result of progression from a preceding upper respiratory tract infection. Therefore, the diagnosis of viral LRTIs in children generally occurs via molecular detection of virus (i.e., PCR) or viral antigens in nasopharyngeal (NP) samples [208, 215]. Detection of these pathogens in lower respiratory tract specimens via bronchoscopy can represent pneumonia, but may also occur in cases of viral shedding, colonization, or contamination from upper respiratory tract secretions. In general, there is good concordance between PCR testing from nasopharyngeal swab and BAL samples for the detection of respiratory viruses [220, 221], limiting the need for more invasive procedures such as bronchoscopy. In fact, studies in children have demonstrated higher yield for detection of respiratory viruses from NP samples compared with BAL [222], although this may reflect the location of

viral replication among various viral pathogens. Therefore, bronchoscopic procedures are reserved for those children with negative testing from upper respiratory tract samples or for whom other nonviral processes are being considered.

Herpesviruses

Herpesviruses are common viral infections that establish life-long latency in human hosts. Herpes simplex virus (HSV), cytomegalovirus (CMV), human herpesvirus-6 and -7 (HHV-6 and HHV-7), Epstein–Barr virus (EBV), and varicella zoster virus (VZV) all have capacity to cause lower respiratory tract infections in the setting of primary infection or reactivation, particularly in severely immunocompromised individuals [223–226]. However, viral shedding is common in both immunocompromised and nonimmunocompromised individuals, and detection of these viruses in the respiratory tract does not confirm disease [209, 210]. Therefore, clinicians utilize bronchoscopic and BAL findings, along with imaging characteristics, to establish herpesviruses as the cause of pulmonary symptoms [223].

Cytomegalovirus

Cytomegalovirus is the most common herpesvirus to cause LRTI and is associated with significant morbidity and mortality in immunocompromised children, most notably solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients [223], as well as patients with HIV/AIDS [224, 225]. Detection of CMV in the blood is common in these patients [227, 228] and does not necessarily indicate CMV disease. Histopathology has been the gold standard for the diagnosis of tissue-invasive CMV disease, demonstrating characteristic nuclear inclusions on biopsied tissue samples [211]. Immunohistochemistry can supplement histopathology, staining for CMV antigens in infected tissue cells and facilitating identification of nuclear enlargement and intranuclear inclusions [211, 229]. Although culture of a lower respiratory tract sample has good specificity for CMV pneumonia, culture does not distinguish between viral shedding and invasive respiratory tract disease [211]. Thus, histopathologic evidence of end-organ damage is preferred for definitive diagnosis of CMV pneumonitis/pneumonia [211].

Polymerase chain reaction (PCR) testing has replaced the use of culture for detection of CMV in clinical specimens. The exquisite sensitivity and negative predictive value of PCR from BAL samples make it a reliable test for ruling out CMV pneumonia [230]. In the correct clinical context, detection of CMV from BAL specimens supports the diagnosis of CMV pneumonia or pneumonitis. Yet, as with culture, mere detection of CMV by PCR cannot distinguish infection from viral shedding in the respiratory tract. Quantification of CMV viral load in BAL specimens, however, may facilitate the distinction between infection and viral shedding [231]. Unlike in blood, higher viral loads correlate with findings on immunohistochemistry staining from lung biopsy samples [229]. CMV quantification from BAL specimens has been predictive of CMV pneumonitis in lung transplant [232, 233] and HSCT recipients [231], as well as in infants [234]. In a seminal study from Boeckh et al., a viral load of 500 IU/mL reliably differentiated CMV pneumonia from asymptomatic shedding in adult HSCT patients [231]. However, the specific viral load associated with CMV pneumonia in pediatric populations has not been established and should not be assumed to be the same as that found in adults. Although the optimal cut-off to distinguish pulmonary infection from respiratory tract shedding varies across studies and patient populations [231–235], quantification of CMV viral load is more specific for CMV infection than detection of CMV by qualitative PCR from respiratory tract specimens.

Herpes Simplex Virus

The incidence of HSV pneumonia in children is not well known. Hypoxemia is the most striking clinical feature of HSV pneumonia, which can be profound [236]. Patients at highest risk include transplant recipients and other immunocompromised patients [236–238], most often from reactivation of latent infection, and mechanically

ventilated patients, who may develop disease as a result of inoculation of contaminated oral secretions [236]. As with CMV, detection of HSV from respiratory tract samples is not diagnostic. In critically ill adults, HSV has been detected by PCR of BAL samples from 30% to 50% of patients [239–241]; the presence of HSV in the respiratory tract of critically ill adults most often represents viral shedding during reactivation and not invasive infection [241]. Histopathology can detect characteristic viral inclusions in cases of HSV pneumonia [236], when biopsies are performed, and more reliably distinguishes tissue-invasive infection from shedding than PCR. The clinical significance of detection of HSV in critically ill children, who have a much lower seroprevalence of HSV than adults, is not known.

In neonates with disseminated HSV, pneumonia may be present in up to 50% of cases [242]. While pneumonia can rarely be the presenting feature [243], the diagnosis of disseminated neonatal infection is made via detection of virus in the blood in combination with systemic symptoms. Bronchoscopy with BAL provides limited added information in these cases and should never delay the initiation of antiviral therapy.

Varicella Zoster Virus

Varicella zoster virus (VZV) can cause severe, life-threatening pneumonia, most often in adults, pregnant women, and immunocompromised individuals [244, 245]. Varicella pneumonia develops almost exclusively in the context of disseminated infection, and tracheal and bronchial ulcers can be visualized on bronchoscopy shortly after the development of skin rash [244, 246]. Because varicella pneumonia is a complication of disseminated disease, and skin lesions are generally present, PCR from skin lesions or blood is likely to diagnose the majority of cases. Respiratory tract specimens are rarely required.

Other Herpesviruses

Epstein–Barr virus, as well as HHV-6 and HHV-7, can be detected on lower respiratory tract samples among immunocompromised and critically ill patients in the setting of viral reactivation [209, 247]. Because the respiratory tract is a common site of EBV latency, viral DNA can be detected in up to 50% of both immune-competent and immune-compromised patients. Given the frequency of EBV, HHV-6, and HHV-7 detection in BAL specimens in both immunocompromised and immunocompetent hosts, the role of these viruses in causing or contributing to lower respiratory tract disease is unknown.

EBV is the causative agent of posttransplant lymphoproliferative disorder (PTLD), which can affect any organ system including the airway. Laryngoscopy and/or bronchoscopy with biopsies can help identify EBV-positive B cells within affected tissues that are characteristic of PTLD [248–250]. Although the airway is a rare site of PTLD, endoscopic procedures may be necessary to confirm the diagnosis.

Human Papillomavirus (HPV)

There are more than 60 serotypes of HPV, which vary in their propensity for human infections. Certain serotypes of HPV can cause recurrent respiratory papillomatosis, a disease consisting of the development of persistent or recurrent epithelial nodules in the airway, most commonly affecting young children and young adults [251]. Clinical symptoms consistent with airway irritation (cough, hoarseness, and voice change) or obstruction (stridor and respiratory distress) may be suggestive of this process. But, definitive diagnosis is made via direct visualization of the lesions via laryngoscopy and/or bronchoscopy [251]; biopsies demonstrate the characteristic papillomas. Medical treatment options are limited (cryotherapy, laser therapy, and intralesional therapies) and surgical approaches may be needed to alleviate obstruction and more debilitating symptoms.

Histopathology/Direct Microscopy

Histopathology is the traditional technique for confirmation of tissue-invasive viral infection. Direct microscopy of respiratory tract specimens is of minimal utility for diagnosing viral infections because viruses cannot be visualized by tra-

ditional microscopic techniques. Histopathology and immunohistochemical staining methods facilitate identification of infiltration of tissues by viral pathogens, including respiratory viruses and herpesviruses [215], by demonstrating characteristic patterns of cellular damage. Respiratory viruses are most often associated with diffuse alveolar damage or interstitial pneumonia [252]; more severe cases may cause necrotizing bronchitis and intra-alveolar hemorrhage. Meanwhile, herpesviruses and adenoviruses cause necrotizing bronchiolitis, as well as the formation of characteristic intranuclear or intracytoplasmic inclusions, which are collections of nucleoproteins and virions [252, 253]. Because the patterns of injury are nonspecific, immunohistochemistry (IHC) or in situ hybridization (ISH) techniques are used to confirm the presence of specific viruses within cells using virus-specific antibodies [252]. Measles virus is characterized by intranuclear and intracytoplasmic eosinophilic inclusions and the presence of multinucleated giant cells [252].

Culture

Viral culture techniques have been utilized traditionally to detect the presence of viruses in clinical samples, including respiratory secretions. Tube culture, which facilitates detection of cytopathic effects in infected cells, and shell-vial culture, which utilizes immunofluorescent techniques to detect viral growth [211, 254], are the approaches most often used for detection of viral pathogens. Shell-vial culture is much faster than tube culture, taking 1–2 days instead of weeks [211]. But, viral cultures are being replaced clinically by the use of molecular detection methods, such as PCR, which are much more sensitive, specific, and cost-effective, and significantly less time-consuming. Because many viruses infect upper airways, while others shed from the oral mucosa or upper respiratory tract, cultures from transbronchial biopsies (i.e., tissue cultures) are more suggestive of viral infection than those performed on BAL fluid.

PCR/Nucleic Acid Testing

Nucleic acid amplification, most often via PCR, has become the diagnostic modality of choice for most viral infections. Multiplex PCR panels can detect the presence of numerous viruses in respiratory tract samples, such as nasopharyngeal (NP) swabs, NP aspirates, induced sputum, or BAL fluid [255]. PCR testing is severalfold more sensitive than culture- and antigen-based methods for detecting viral pathogens in respiratory samples [215]. There is good concordance between PCR testing from NP swabs and BAL samples for the detection of respiratory viruses [220, 221], making NP samples the preferred diagnostic specimens in children when these common viral pathogens are being considered. Because of the potential for prolonged viral shedding following an infection, and because viruses can colonize airways, as well, detection of viral DNA by PCR needs to be interpreted in the appropriate clinical and epidemiologic contexts to support a diagnosis of viral pneumonia.

Antigen-Based Testing

Immunofluorescent techniques (immunochromatographic testing) or enzyme immunoassay (EIA) tests can rapidly detect viral antigens in respiratory specimens, most often NP samples. Test results are available in minutes, making them highly valuable point-of-care tests. Rapid antigen testing for influenza and RSV (target: RSV fusion surface protein) are commercially available and the most common rapid viral tests used in children [256]. Antigen detection is influenced by the viral load present in the sample, so rapid antigen detection tests tend to be less sensitive than PCR [215, 257]. A 2015 meta-analysis by Chartrand and colleagues reported a pooled sensitivity and specificity of RSV rapid antigen tests of 80% (95% CI: 76–83%) and 97% (95% CI: 96–98%), respectively [257]. These authors performed a separate meta-analysis evaluating

the performance of rapid influenza testing [258], reporting a pooled sensitivity of 62.3% (95% CI: 57.9–66.6%) and specificity of 98.2% (95% CI: 97.5–98.7%). Thus, rapid antigen tests perform well for ruling in RSV and influenza infections, but less well for ruling them out.

Mycology

Introduction

Infection of the respiratory tract is the most common form of invasive fungal disease (IFD) in children. Yeasts, molds, and dimorphic fungi (organisms that can grow as either a yeast or mold) are ubiquitous in the environment and cause infection of the paranasal sinuses and/or lungs following inhalation of fungal spores [259], although fungi can also disseminate hematogenously, leading to secondary pulmonary infections. Immunecompromised individuals and those with impaired airway clearance, such as with cystic fibrosis, are most prone to pulmonary IFD.

In order to facilitate the use of consistent terminology in clinical and epidemiologic research, consensus guidelines from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) categorize the diagnosis of IFD into proven (Fig. 9.2), probable (Fig. 9.3), or possible cases [260]. Proven cases require histologic evidence or positive microbiologic culture from sterile site body fluids or tissue specimens [260]. This does *not* include BAL fluid or sputum. Meanwhile, the diagnosis of probable or possible IFD, which are terms used only in immunecompromised individuals, requires a combination of host factors and clinical features with (for probable) or without (for possible) mycological evidence of infection [260]. The EORTC/MSG definitions are commonly employed in research; however, it is important to recognize that they are generally not employed in clinical practice. Failure to meet these definitions does not exclude a diagnosis of IFD, and the definitions have variable sensitivity and specificity compared to histopathology in children [261]. So, while these terms promote the use of consistent terminology in the research setting, they should not be employed clinically or relied upon to guide treatment decisions. They nevertheless form the basis for many studies referred to in the following sections.

Analysis and specimen	Molds[a]	Yeasts[a]
Microscopic analysis: sterile material	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells–for example, *Cryptococcus* species indicated by encapsulated budding yeasts or Candida species showing pseudohyphae or true hyphae[c]
Culture		
Sterile material	Recovery of a mold or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding bronchoalveolar lavage fluid, a cranial sinus cavity specimen, and urine	Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 h ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process
Blood	Blood culture that yields a mold[d] (e.g., *Fusarium* species) in the context of a compatible infectious disease process	Blood culture that yields yeast (e.g., *Cryptococcus or Candida* species) or yeast-like fungi (e.g., *Trichosporon* species)
Serological analysis: CSF	Not applicable	Cryptococcal antigen in CSF indicates disseminated cryptococcosis

[a] If culture is available, append the identification at the genus or species level from the culture results.
[b] Tissue and cells submitted for histopathologic or cytopathologic studies should be stained by Grocott-Gomorri methenamine sliver stain or by periodic acid Schiff stain, to faciliate inspection of fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be stained with a fluorescent dye (e.g., calcofluor or blankophor),
[c] *Candida, Trichosporon, and yeast-like Geotrichum species and Blastoschizomyces capitatus* may also from pseudohyphase or true hyphae.
[d] Recovery of *Aspergillus* species from blood cultures invariably represents contamination.

Fig. 9.2 Criteria for proven invasive fungal disease except for endemic mycoses. (Reprinted with permission from De Pauw et al. [260]. © 2008 by the Infectious Diseases Society of America)

Host factors[a]
- Recent histroy of neutropenia (<0.5 x 10^9 neutrophils/L [<500 neutrophils/mm^3] for > 10 days) temporally related to the onset pf fungal disease
- Receipt of an allogeneic stem cell transplant
- Prolonged use of corticosteriods (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for >3 weeks
- Treatment with other recongined T cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies (such as alemutuzumab), or nucleoside analogues during the past 90 days
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)

Clinical criteria[b]
- Lower respiratory tract fungl disease[c]
  - The presence of 1 of the following 3 signs on CT:
    - Dense, well-circumscribed lesions(s) with or without a halo sign
    - Air-crescent sign
    - Cavity
- Tracheobronchitis
  - Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
- Sinonasal infection
  - Imaging showing sinusitis plus at least 1 of the following 3 signs:
    - Acute localized pain (including pain radiating to the eye)
    - Nasal ulcer with black eschar
    - Extension from the paranasal sinus across bony barriers, including into the orbit
- CNS infection
  - 1 of the following 2 signs:
    - Focal lesions on imaging
    - Meningeal enhancement on MRI or CT
- Disseminated candidiasis[d]
  - At least 1 of the following 2 entities after an episode of candidemia within the previous 2 weeks:
    - Small, target-like abscesses (bull's-eye lesions) in lover or spleen
    - Progressive retinal exudates on ophthalmologic examination

Mycological criteria
- Direct test (cytology, direct microscopy, or culture)
  - Mold in sputum, bronchoalveolar lavage fluid, bronchial brush, or sinus aspirate samples, indicated by 1 of the following:
    - Presence of fungal elements indicating a mold
    - Recovery by culture of a mold (e.g., *Aspergillus, Fusarium,* Zygomycetes, or Scedosporium species)
- Indirect tests (detection of antigen or cell-wall consistuents)[e]
  - Aspergillosis
    - Galactomannan antigen detected in plasma, serum, bronchoalveolar lavage fluid, or CSF
  - Invasive fungal disease other than cryptococcosis and zygomycoses
    - β-D-glucan detected in serum

NOTE. Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion, Cases that meer the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

[a] Host factors are not synonymous with risk factors and are characteristics by which individuals predisposed to invasive fungal disease can be recognized. They are intended primarily to apply to patients given treatment for malignant disesase and to recipients of allogeneic hematopoietic system cell and solid-organ transplants, These host factors are also applicable to patients who receive corticosteroids and other T cell suppressants as well as to patients with primary immunodeficiencies.

[b] Must be consistent with the mycological findings, if any and must be temporally related to current episode.

[c] Every reasonable attempt should be made to exclude an alternative etiology.

[d] The presence of signs and symptoms consistent with sepsis syndrome indicates acute disseminated diseses, wherease their absence denotes chronic disseminated disease.

[e] These tests are primary applicable to aspergilosis and candidasis and are not useful in diagnosing infections due to *Cryptococcus* species or Zygomycetes (e.g., *Rhizopus, Mucor, or Absidia* species). Detection of nucleic acid is not included, because there are as yet no validated or standardized methods.

Fig. 9.3 Criteria for probable invasive fungal disease except for endemic mycoses. (Reprinted with permission from De Pauw et al. [260]. © 2008 by the Infectious Diseases Society of America)

Fungi That Cause Pulmonary Infections

Aspergillus

Aspergillus species cause a myriad of clinical pulmonary presentations ranging from asymptomatic colonization to ABPA and invasive pulmonary aspergillosis (IPA). Following inhalation, *Aspergillus* species colonize the upper and lower airways. Colonization of a preexisting pulmonary cavity may lead to the formation of a fungus ball, which could remain asymptomatic for prolonged periods or cause symptoms such as cough or hemoptysis. ABPA is an allergic response to *Aspergillus fumigatus* antigens that primarily affects patients with asthma or cystic fibrosis [262, 263]. Characterized by recurrent episodes of wheezing, cough, transient pulmonary opacities, and bronchiectasis, the diagnostic criteria for ABPA are based on cutaneous hypersensitivity to *A. fumigatus* antigens, serum IgE levels (>1000 IU/mL), and two out of three of the following: presence of precipitating or IgG antibodies against *A. fumigatus* in serum, radiographic pulmonary opacities consistent with ABPA, and a total eosinophil count >500 cells/μL [264].

Invasive pulmonary aspergillosis is the most common manifestation of invasive aspergillosis (IA) and is associated with significant morbidity and mortality [265, 266]. IPA may manifest as nodular pulmonary infiltrates, pleural-based infiltrates, or cavitary lesions, and dissemination secondary to vascular invasion also occurs. Tracheobronchitis is a relatively rare form of IA that most often affects lung transplant recipients and severely immunocompromised individuals [267]. Infiltration of the bronchial or tracheal mucosa leads to ulceration, necrosis, and/or the formation of pseudomembranes, which can be visualized on bronchoscopy and confirmed by biopsy and culture [267].

The diagnosis of aspergillosis is based on clinical signs and symptoms, including imaging findings, combined with diagnostic testing. *Aspergillus* species do not grow efficiently in culture and can be morphologically similar to other molds on histologic examination [268]. Thus, confirmation of aspergillosis can be challenging. Culture remains the gold standard for confirmation of IPA, but the use of biomarkers (serum or BAL galactomannan; see below) and molecular testing (PCR, florescent in situ hybridization [FISH]) can support its diagnosis and provide more rapid information than culture.

Pneumocystis jirovecii

Pneumocystis jirovecii is a leading cause of opportunistic infection in immunocompromised patients worldwide [269]. *Pneumocystis jirovecii* pneumonia (PJP) is a rare diagnosis in children but remains an important consideration in neonates and immune-compromised or immune-suppressed pediatric populations [270]. Airway colonization is transient early in life: in a longitudinal study of 46 mother–infant pairs, 91% of infants had *Pneumocystis* identified by PCR from nasopharyngeal swabs within the first 6 months of life [271]. While colonization precedes the development of infection, it is unclear how often colonization progresses to infection versus infection which develops following new acquisition.

Clinical symptoms of PJP are highly variable and often nonspecific. In patients with HIV, PJP typically presents with subacute symptoms consisting of nonproductive cough, low-grade fever, and progressive dyspnea [269, 272], while symptoms can be more acute in non-HIV patients. Hypoxia is the most frequent sign of PJP, and the magnitude of the alveolar-arterial oxygen gradient often signals the severity of disease [269]. Chest radiographs are normal early, but frequently show symmetric, perihilar interstitial infiltrates later in the course [273]. Figure 9.4 displays the characteristic chest x-ray of an 8-month-old boy with PJP. Chest CT is the imaging modality of choice, most often showing patchy, ground-glass infiltrates [269, 273].

Pneumocystis cannot be grown in standard culture; therefore, diagnosis relies on direct microscopy, histologic evaluation, or DNA detection. Silver stain (Grocott-Gomori methenamine

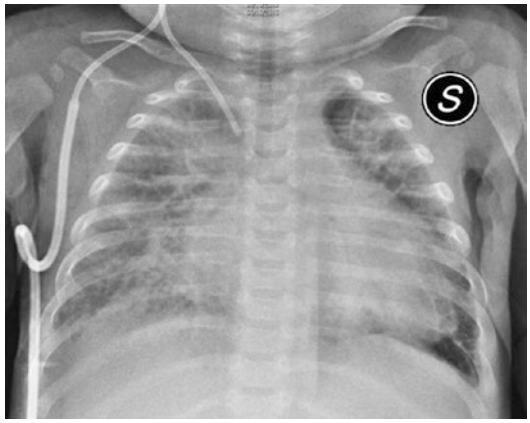

Fig. 9.4 *Pneumocystis jirovecii* pneumonia in an 8-month-old boy after bone marrow transplantation. Chest radiograph demonstrates bilateral interstitial infiltrates and patchy consolidation on the left side (S). (Reprinted with permission from Toma et al. [273]. © Springer-Verlag Berlin Heidelberg 2016)

silver stain) is the conventional method for identifying organisms, but other staining methods are also useful [269, 272]. Immunofluorescent techniques have been used to identify *Pneumocystis* [269, 274], but are labor intensive and do not outperform direct microscopy [275]. PCR from BAL is becoming the test of choice for PJP as numerous studies have demonstrated excellent sensitivity [276, 277]. (1 → 3)-β-D-glucan (BDG) is a cell wall component of many fungi, including *Pneumocystis.* BDG detection in serum or plasma has excellent sensitivity (94.8%) and good specificity (86.3%) in the diagnosis of PJP [278], but its specificity from BAL samples is low.

Candida

Candida lung disease most often develops secondary to hematogenous dissemination. This form of candidiasis typically has a diffuse, nodular pattern on imaging, consistent with hematogenous spread of infection [279]. Meanwhile, *Candida* species rarely cause primary LRTI. Colonization of the airways occurs quickly following endotracheal intubation [280]. Therefore, *Candida* are frequently recovered on culture from tracheal aspirate or BAL samples of critically ill patients, but seldom are the cause of pneumonia [281, 282]. Similarly, *Candida* are commonly recovered from sputum samples in patients with cystic fibrosis [283], yet the precise role of *Candida* in the lung disease of these patients has not been established.

Cryptococcus

Cryptococcus neoformans and *Cryptococcus gattii* are budding yeasts found in soil worldwide and are particularly important pathogens in immunocompromised hosts, most notably those with HIV. Cryptococcal lung disease occurs in both immune-compromised and immune-competent individuals [284, 285], but is rare in children. In a population-based study of cryptococcosis in the United States from 2000 to 2007, the rate of hospitalization in children was less than 0.25 per 100,000 population [286]; the specific rate of respiratory cryptococcosis was not reported. At Beijing Children's Hospital, there were 53 children hospitalized with cryptococcal disease from 2002 to 2014, half of whom had pulmonary involvement [287].

Cryptococcal species can be grown readily on bacterial or fungal culture media, and isolation from respiratory tract samples may support a diagnosis of cryptococcosis since these fungi are not typical respiratory tract flora [288]. Latex agglutination and EIA tests are available that can detect the capsular polysaccharide of both *C. neoformans* and *C. gattii* [289]. Cryptococcal antigen testing from serum and cerebrospinal fluid is sensitive for the detection of cryptococcal meningitis and disseminated cryptococcosis, but has lower sensitivity in non-CNS infections [290, 291]. Cryptococcal antigen testing from BAL fluid has limited sensitivity and positive predictive value, which does not support its use clinically [292–294].

Mucorales Species

Fungi of the subphylum Mucormycotina, the vast majority of which are in the order Mucorales, are ubiquitous, filamentous fungi found in soil and

decaying matter throughout the world [295]. Invasive infections, known as mucormycosis (formerly zygomycosis), are predominantly acquired through inhalation, but also can develop following direct inoculation of skin or mucosal surfaces [295]. Pulmonary mucormycosis develops most often as a result of inhalation of fungal spores, but can occur as an extension of sinus disease or secondary to disseminated disease. Clinically, pulmonary mucormycosis is similar to other mold infections, such as aspergillosis. Due to angioinvasive nature of Mucorales, dissemination is common (>50%), although blood cultures are rarely positive.

Diagnosis of pulmonary mucormycosis is challenging. Abnormal chest imaging in the correct host (neutropenia, transplant recipient, and diabetes with ketoacidosis) should key clinicians to the possibility of this infection. The imaging findings are nonspecific, varying from discrete solitary nodules to larger areas of confluent infection to cavitary lesions with pulmonary effusion [296]. Bronchoalveolar lavage is an important diagnostic tool in high-risk patients with imaging findings consistent with mucormycosis, facilitating identification by histopathology and culture. Mucorales have broad, thin-walled, irregular, pauci-septate hyphae with wide-angled (90°) branching on microscopic examination, which distinguishes them from other molds, such as *Aspergillus* or *Fusarium* species [275, 296]. Definitive diagnosis is made by culture, although the sensitivity of culture is poor [296]. Molecular tests, such as PCR, are not routinely clinically available for Mucorales species, and antigen tests, such as β-D-glucan and galactomannan, are not clinically useful.

Dimorphic Fungi

Dimorphic fungi are comprised of a group of fungi that can exist in either yeast or mycelial (mold) forms, depending on temperature and environmental conditions: *Blastomyces* species (*B. dermatitidis, B. gilchristii*), *Coccidioides* species (*C. immitis*, *C. posadasii*), *Histoplasma capsulatum*, *Paracoccidioides* species (*P. brasiliensis*, *P. lutzii*), *Sporothrix schenckii*, and *Talaromyces marneffei* (formerly *Penicillium marneffei*). The mold phase allows these organisms to survive in the environment, while the yeast phase promotes virulence, immune evasion, and development of human infections [297, 298]. These organisms, often referred to as endemic mycoses, are geographically limited and found in specific ecologic niches within their endemic areas. Histoplasmosis, coccidioidomycosis, and blastomycosis are the most likely to manifest as pulmonary infections [298]. In the United States, histoplasmosis occurs predominantly in the Midwest and Southeast, as does blastomycosis, while coccidioidomycosis occurs in the Southwest [299]. Paracoccidioidomycosis is a cause of CAP in Central and South America [300].

Pulmonary infection by endemic mycoses follows inhalation of aerosolized mycelial forms of the fungi. The majority of infections are self-limited, but more severe manifestations, including death, can occur in the setting of a large inoculum of infection or in an immune-compromised individual [301, 302]. Acute pulmonary infections typically present as focal, consolidative processes, similar to CAP in their symptomatology and radiographic appearance [297, 301, 303]. Additional nonspecific symptoms such as fatigue, arthralgias/myalgias, and chills commonly accompany this stage of infection. Mediastinal and hilar adenopathy are often seen on radiographs in patients with acute histoplasmosis and to a lesser degree in patients with coccidioidomycosis [304].

For all endemic mycoses, the definite diagnosis is made by identifying fungi on histopathology, cytopathology, or culture. Histoplasmosis is associated with the formation of caseating and noncaseating granulomas [302, 305]. Serologic tests (complement fixation, immunodiffusion) are available to aid in the diagnosis of blastomycosis, coccidioidomycosis, and histoplasmosis, but have variable sensitivity depending on the form of disease and duration of infection. Histoplasma antigen testing by EIA can be performed on urine, blood, and BAL fluid, but it is positive not only in cases of histoplasmosis but

also infections caused by *Blastomyces, Paracoccidioides,* and *Talaromyces marneffei* [306]. Antigenuria and antigenemia are more often detected in cases of disseminated infection than in patients with isolated pulmonary infections [304, 307].

Methods to Diagnose Fungal Pulmonary Infections

Histopathology/Direct Microscopy

Direct microscopy of BAL or lung tissue specimens is often the first test performed when pulmonary fungal infection is suspected [275]. Although less sensitive than culture, positive direct microscopy is helpful since growth of fungi in culture can take days to weeks. Many fungi can be identified based on their morphologic characteristics (Table 9.2), although not to the species level [289]. Use of 10–20% potassium hydroxide (KOH) facilitates identification of fungi by degrading proteins within specimens with the exception of fungal cell walls, promoting visualization of hyphae and conidia [275]. The addition of other stains, such as Calcofluor white, can further augment identification of fungi. The most sensitive stain used to identify fungi in tissue and BAL fluid specimens is Grocott-Gomori methenamine silver (GMS), which stains almost all fungal cell walls [259]. GMS (aka "silver") stain is the conventional method for identifying *Pneumocystis* organisms from sputum or BAL fluid samples [269, 272], as well as Mucorales, *Aspergillus*, and other fungi that cause invasive disease [275, 296]. Periodic acid Schiff (PAS) stains are also useful for detecting fungal hyphae [289].

Culture

Culture is the primary method for diagnosing pulmonary IFD, supporting speciation of organisms and antimicrobial susceptibility testing, when possible [289]. Culture is more sensitive than direct microscopy [275] and should be routinely performed on all BAL specimens when fungal infection is considered. Special fungal media are often utilized, which contain antibiotics to inhibit growth of bacteria. Several fungi, particularly molds, do not readily grow in culture and yield may be as low as 30–50% even when visualized by histologic and cytologic examination [308]. *Pneumocystis jirovecii* cannot be grown in routine culture; therefore, diagnosis relies on direct microscopy, histologic evaluation, or DNA detection in respiratory samples [269].

Bronchoalveolar lavage is an important diagnostic tool in patients at high risk for pulmonary IFD. Because the pathogenesis of primary pulmonary IFD involves inhalation of fungal spores, colonization of the airway necessarily precedes infection. Therefore, culture in itself is insufficient to establish the diagnosis of pulmonary IFD with any fungal organism. Culture must be combined with the clinical features (symptoms, imaging findings) and host factors to make a definitive diagnosis [260].

PCR/Nucleic Acid Testing

PCR testing is clinically available for select fungi: *Candida, Aspergillus,* and *Pneumocystis jirovecii.* Distinguishing between colonization and invasive infection is a major limitation of use of PCR from BAL for each of these fungi, however. In the appropriate clinical context, identification of *Aspergillus* or *Pneumocystis* by PCR from BAL fluid increases the posttest probability of invasive infection and may assist clinicians when other diagnostic tests (i.e., culture) are negative.

PCR has become a valuable tool in the diagnosis of invasive aspergillosis (IA), most often when performed on serum or whole-blood samples. Unfortunately, data in pediatric patients are limited. A 2016 meta-analysis in pediatric cancer and HSCT patients reported a pooled diagnostic performance of PCR for screening of IA: specificity 43–85%, sensitivity 11–80%, positive predictive value (PPV) 20–50%, and negative predictive value (NPV) 60–96% [309]. Meanwhile, the performance of PCR for the

Table 9.2 Diagnostic features of fungi associated with respiratory tract infections

Organism	Microscopic characteristics
Yeasts	
Cryptococcus spp. (*C. neoformans, C. gattii*)	Spherical budding yeasts of variable size, 2–15 μm in diameter. Capsule may be present or absent. No hyphae or pseudohyphae. Stain red with Mayer's mucicarmine stain; India ink stain used for cerebrospinal fluid samples
Pneumocystis jirovecii	Cysts are round, collapsed, or crescent shaped. Trophozoites seen on staining with Giemsa, methenamine silver (GMS), or immunofluorescent stains
Trichosporon	Hyaline arthroconidia, blastoconidia, and pseudohyphae, 2–4 by 8 μm
Molds	
Hyaline hyphomycetes (*Aspergillus, Acremonium, Fusarium, Paecilomyces, Phialemonium, Scedosporium, Scopulariopsis, Trichoderma*)	Hyaline, septate dichotomously branching (45° angle) hyphae of uniform width (3–6 μm)
Mucorales (*Absidia, Cunninghamella, Mucor, Rhizomucor, Rhizopus, Saksenaea*)	Broad, thin-walled, pauci-septate hyphae, 6–25 μm wide with nonparallel sides and random branches (90° angle)
Dematiaceous hyphomycetes (*Alternaria, Bipolaris, Curvularia, Cladophialophora, Dactylaria, Exophiala, Phialophora, Ramichloridium, Wangiella)*	Pigmented (brown, tan, or black), septate hyphae, 2–6 μm wide
Dimorphic fungi	
Blastomyces dermatitidis	Large (8–15 μm diameter) thick-walled budding yeast cells. The junction between mother and daughter cells is typically broad-based. Cells may appear multinucleate. Occasionally stains red with Mayer's mucicarmine stain
Coccidioides spp. (*C. immitis, C. posadasii*)	Spherical, thick-walled spherules, 20–30 μm diameter. Mature spherules contain small, 2–5 μm diameter endospores. Released endospores may be mistaken for yeast. Arthroconidia and hyphae may form in cavitary lesions
Histoplasma capsulatum	Small (2–4 μm diameter), intracellular, budding yeasts. Associated with caseating granulomas
Paracoccidioides brasiliensis	Large (2–30 μm diameter), multiple-budding yeasts. 12 or more narrow neck buds of variable size may arise from the mother cell, daughter yeasts may be in a "pilot-wheel configuration"
Penicillium marneffei	Oval, intracellular yeast cells bisected with a septum (fission yeast)
Sporothrix schenckii	Elongated or "cigar-shaped" yeast cells of varying size (rare). Tissue reaction forms asteroid bodies

Adapted with permission from Lease and Alexander [275] © Thieme Medical Publishers, 2011

diagnosis of IA during febrile periods was highly variable across studies: specificity 36–83%, sensitivity 0–100%, PPV 0–71%, and NPV 88–100% [309]. The sensitivity of *Aspergillus* PCR is negatively affected by the administration of antifungal therapy [310], which is relevant considering that many patients with suspected IPA are receiving antifungal prophylaxis at the time.

In patients undergoing bronchoscopy, pathogen-specific PCR testing may be valuable. In a systematic review by Avni, the diagnostic performance of PCR in BAL fluid for diagnosing proven/probable IPA was similar to that of galactomannan (sensitivity 82–86%, specificity 95%), while the sensitivity of either test being positive increased to 97% (95% CI 83–99.5) [311]. Numerous studies have reported excellent performance of PCR from BAL samples for the diagnosis of *Pneumocystis* pneumonia – pooled sensitivity of 98% and specificity of 91–93% – making it a highly useful test [21, 22]. Although several authors have suggested that quantitative

PCR can help differentiate active infection from colonization [23–25], the fungal load varies among different patient populations (i.e., HIV- vs non-HIV-infected patients, adults vs children) and threshold values that distinguish infection from colonization have not been clearly established, especially in children.

Panfungal PCR, which uses primers targeting the internal transcribed spacer (ITS) 1 and/or 2 region, can identify the presence of fungi within clinical samples. This approach is particularly useful in instances when fungi are visualized microscopically within specimens, but cultures are nondiagnostic. Because of the presence of colonizing flora within respiratory tract samples, panfungal PCR may have higher accuracy from tissue specimens, as opposed to BAL samples [312]. Next-generation sequencing also has the potential to identify fungi within culture-negative specimens, but it is best served from a sterile-site rather than respiratory tract samples.

Antigen-Based Testing

Histoplasma capsulatum antigen can be detected by EIA in serum, urine, and BAL fluid specimens in patients with histoplasmosis [305]. Antigen detection is both a rapid and sensitive adjunctive testing method for the diagnosis of histoplasmosis, although cross-reactivity occurs with other endemic mycoses including *Blastomyces*, *Paracoccidioides,* and *Talaromyces marneffei* [306]. Urine antigen detection is more sensitive in disseminated histoplasmosis than in primary pulmonary infection. In a multicenter study of patients with histoplasmosis, antigen was detected in the urine of 145 of 158 (91.8%) patients with disseminated histoplasmosis, but only 19 of 50 (38.0%) cases with acute or subacute pulmonary infections [307]. Antigen detection from BAL is more sensitive than blood or urine testing in patients with pulmonary histoplasmosis. In a study by Hage et al. that included 31 patients with pulmonary histoplasmosis, the diagnostic performance of *Histoplasma* antigen detection in BAL fluid for the diagnosis of histoplasmosis was as follows: sensitivity 93.5%, specificity 97.8%, PPV 69.1%, and NPV 99.7% [313].

Several commercially available latex agglutination and EIA tests have been developed for detection of cryptococcal polysaccharide capsule antigen, both of *C. neoformans* and *C. gattii* [289]. These tests are predominantly performed in serum and cerebrospinal fluid samples. The sensitivity of serum cryptococcal antigen is higher in individuals with disseminated and central nervous system (CNS) infection than in those with isolated lung disease [290, 291]. In a report of HIV-negative adult patients with cryptococcal disease, only 56% of 71 patients with pulmonary disease had a positive serum cryptococcal antigen test compared to 87% of those with CNS infection [290]. Cryptococcal antigen testing from BAL fluid has demonstrated variable sensitivity (71–100%) and poor positive predictive value (36–67%) in adults [292–294]. The performance of cryptococcal antigen on BAL fluid in children is unknown, but its usefulness is likely narrow considering the rarity of cryptococcal pneumonia in children.

Galactomannan

Galactomannan (GM) is a cell-wall component of *Aspergillus* species [289]. Detection of GM in serum or BAL fluid samples using ELISA is an indirect test that can support the diagnosis of IPA [260]. While GM is generally specific to aspergillosis, it can also be detected in serum of patients with penicilliosis [314]. Additionally, false-positive results have been reported in patients treated with aminopenicillin/β-lactamase combination agents [315].

In adults, serum and BAL GM correlate significantly in patients with IPA [316, 317]. An optical density index of ≥0.5 from either serum or BAL fluid is most often used as the cut-off for a diagnosis of IPA. However, BAL GM has been reported to have a higher sensitivity but lower specificity than serum GM [318–321]; therefore, some authors have suggested using a higher GM cut point from BAL fluid should to limit false-positive results [321, 322].

Data on GM from BAL fluid in pediatric patients are limited. de Mol et al. retrospectively evaluated the performance of GM from BAL fluid among 41 cases of proven/probable IA and found that a GM ≥0.5 had a sensitivity, specificity,

PPV, and NPV of 82%, 88%, 82%, and 87%, respectively [316]. Similarly, Mohammadi and colleagues found that a BAL fluid GM ≥0.5 had a sensitivity and positive predictive value of 87.5% and 93.3% [323]. Meanwhile, Desai et al. reported that a cut-off value of ≥0.5 had a sensitivity for proven/probable IA of 78% and a specificity of 84% among their pediatric cohort, while a cut-off value of 0.87 had sensitivity of 78% and specificity of 100% among a subset of immunocompromised children [317]. Additional studies are needed to establish the optimal cut-off of GM from BAL fluid in pediatric patients, but GM appears to be a valuable adjunctive test to support a diagnosis of IPA in children.

β-D-glucan

(1 → 3)-β-D-glucan (BDG) is a cell wall component of many fungi and is considered an indirect test of probable IFD with these fungi [260]. BDG is a cell component of *Candida*, *P. jirovecii*, *Aspergillus*, *Fusarium* species, *Trichosporon, Coccidioides, Histoplasma*, and others, but not of *Cryptococcus* or Mucorales [289]. There are several different available assays, but only Fungitell® (Associates of Cape Cod, Inc., East Falmouth, MA) is FDA approved for use in serum; no assays are FDA approved for testing of BAL samples. A threshold of ≥80 pg/mL is considered positive on the Fungitell® assay (product label), although other thresholds have been reported to have better diagnostic accuracy [324]. False-positive BDG results can occur in patients receiving albumin, intravenous immunoglobulin (IVIG), and other blood products [325–327].

Unfortunately, there are limited data regarding the diagnostic performance of serum BDG in children. With a high NPV, serum BDG is most valuable in excluding IFD in high-risk patients, including neonates, rather than identifying patients with true fungal infections [309, 328, 329]. A recent meta-analysis identified three studies in pediatric cancer or HSCT patients [309]. Among 226 children, 38 were diagnosed with proven/probable IFD and the diagnostic performance of BDG across these studies was as follows: sensitivity 50–83%, specificity 29–82%, PPV 17–49%, and NPV 84–96% [309].

BDG testing from BAL specimens is a potentially appealing approach to the diagnosis of pulmonary IFD. However, since airway colonization with fungi is common, results of studies have been poor. A meta-analysis of six adult studies that included 838 patients, 138 of whom had proven or probable IFD, found that BDG from BAL specimens had marginal diagnostic value [330]: pooled sensitivity of 52% and specificity of 58%. Salerno et al. reported that BAL BDG was inferior to serum BDG for the diagnosis of PJP in a cohort of 119 patients with HIV [331]. Based on available data, performance of BDG from BAL specimens does not appear to add value to serum BDG testing.

Parasitology

Introduction

Parasitic infections are extremely common in children around the world, especially in warm, low-income countries where sanitation is poor and housing is crowded [332]. Parasites can be classified as either protozoa (unicellular organisms) or helminths (multicellular worms), which are further categorized as nematodes (roundworms), cestodes (tapeworms), or trematodes (flukes). Most parasitic infections are acquired through the fecal–oral route, but several are vector borne, such as *Plasmodium* spp. (malaria) and *Trypanosoma* spp. (Chagas disease, African sleeping sickness) [333]. The frequency with which parasitic infections manifest pulmonary symptoms, and would be amenable to diagnosis via bronchoscopy, is highly variable across the myriad of organisms that cause human infections.

Many protozoan infections have pulmonary manifestations as the result of the disseminated forms of the disease: *Plasmodium* spp. [334], *Toxoplasma gondii* [335–338], *Leishmania* spp. [339], *Entamoeba histolytica* [340, 341], *Babesia* spp. [342], and *Trypanosoma* spp. [343]. In most cases, the pulmonary signs/symptoms are the indirect result of tissue damage (pneumonitis, pulmonary edema, pulmonary effusion,

and acute respiratory distress syndrome) rather than primary pulmonary disease [343]. However, some protozoa have been associated with bronchopulmonary infections directly. *Toxoplasma gondii* and other protozoa, such as *Balantidium coli*, *Cryptosporidium* spp., and *Microsporidium* species, have been reported as causes of pneumonia in immune-compromised individuals [336–338, 344–348]. *Entamoeba histolytica* has a predilection to form extra-intestinal abscesses, which can involve the lung [340], most often from extension of an amebic liver abscess [341]. Extremely rare cases of bronchopulmonary infections have also been reported with *Lophomonas blattarum* [349–351], a protozoa uncommonly associated with human disease. In very rare instances, ingestion and/or aspiration of free-living amoeba (*Acanthamoeba* spp., *Balamuthia mandrillaris*) can result in invasive respiratory tract infection [352].

All helminths have life cycles that include an egg, larval (one or more), and adult stages [332]. Entry into the human body occurs in one of three ways: ingestion of eggs or larvae, direct inoculation of skin either by larvae, or through an arthropod vector [332]. When direct or arthropod inoculation occurs, larvae enter the systemic circulation eliciting eosinophilic inflammation in various tissues, including the lung [343, 353, 354]. Similarly, after acquisition via ingestion, larvae can penetrate intestinal mucosa and enter the bloodstream, or they can migrate directly to the lung or pleura [343, 353, 354]. An example of the helminthic life cycle is shown for *Necator americanus* in Fig. 9.5 [355]. As the larvae migrate through the lung, eosinophilic pneumonia or pneumonitis may develop, a condition called Loeffler syndrome [356]. Accompanying symptoms include cough, wheezing, and fever, and peripheral eosinophilia is common [356].

Several helminthic infections are associated with pulmonary manifestations (Table 9.3). *Schistosoma mansoni* [357, 358], *Ancylostoma duodenale* [354], *Necator americanus* [354], *Dirofilaria immitis* [359, 360], *Toxocara* species [361, 362], *Paragonimus* spp. [363], *Ascaris lumbricoides* [364], and the agents that cause filariasis (*Wuchereria bancrofti, Brugia malayi*) [353, 365] can induce diffuse, eosinophilic inflammatory responses that manifest as pulmonary symptoms (wheezing, cough). *Echinococcus* species form cysts, which are most often asymptomatic when present in the lung. However, cysts can manifest pulmonary symptoms as a result of airway compression or due to hypersensitivity reactions when they rupture [366–368]. *Ascaris lumbricoides* [369] rarely causes direct pulmonary infections following aspiration, although ascension of adult intestinal *Ascaris* roundworms from the esophagus can lead to tracheal obstruction and respiratory distress [370, 371]. *Strongyloides stercoralis* infections are generally limited to the intestinal lumen in immune competent individuals, but may cause a mild, transient respiratory illness secondary to Loeffler syndrome [356]. In immune-compromised patients, particularly those receiving steroids, a life-threatening hyperinfection syndrome can develop in individuals with *Strongyloides* intestinal infection/colonization in which the organisms penetrate the intestinal lining and migrate to numerous tissues including the lungs [372]. In this setting, larvae and adult parasites may be detected on BAL fluid [373, 374]. *Trichinella spiralis*, acquired from ingestion of undercooked pork, can form diaphragm and accessory muscle abscesses/infection leading to respiratory effort weakness and pulmonary symptoms, but does not directly cause lung infection [375].

While most parasitic infections are confined to the gastrointestinal lumen, many species invade the bloodstream as part of their life cycle [332, 333]. These infections can induce eosinophilic inflammation either systemically or locally after migrating to the lungs [354]. Protozoa can also cause disseminated infections that are associated with pulmonary manifestations, such as acute respiratory distress syndrome and pulmonary edema [343]. As a result, pulmonary symptoms accompany parasitic infections at varying frequency. Because few parasites cause solely pulmonary disease, bronchoscopy is a relatively limited tool in the diagnosis of parasitic infections. Diagnosis of parasitic infections is most often made via direct examination of stool or blood, or via serology [332]. The Center for Disease Control

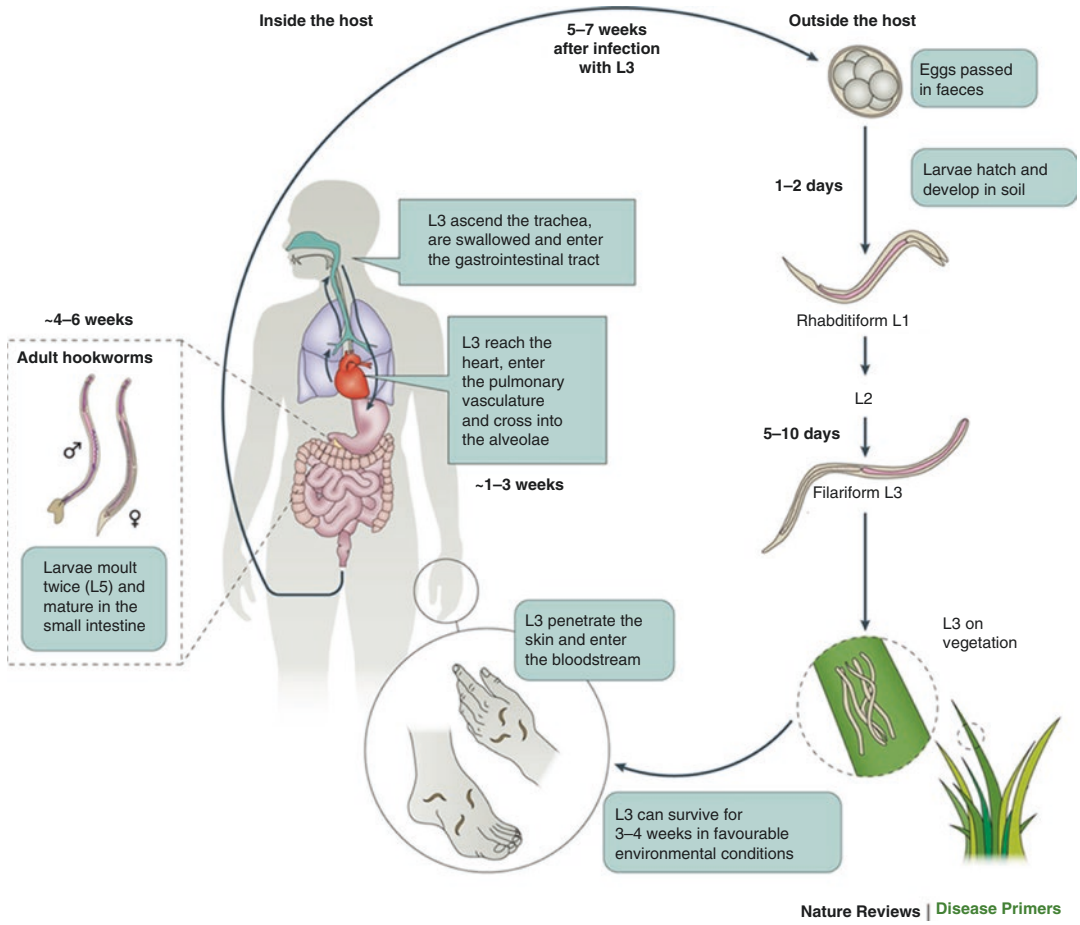

Fig. 9.5 Life cycle of *Necator americanus.* Hookworm eggs hatch in soil and rhabditiform (early) larvae molt twice (first-stage larvae (L1) and L2) before becoming infective (L3). L3 accumulate in soil or on grass awaiting exposure to human skin (often the hands, feet, or buttocks), which they can penetrate. L3 then make their way to the peripheral vasculature, where they are passively swept within the bloodstream, first to the right side of the heart and then to the pulmonary vasculature. In the lungs, L3 exit from the alveolar capillaries into the bronchial tree, which they ascend to reach the pharynx, from which they enter the gastrointestinal tract to finally complete their migration to the small bowel. Once in the duodenum, immature L5 hookworms use "teeth" (*Ancylostoma* spp.) or cutting plates (*Necator* spp.) that line their buccal capsule to lacerate the mucosa and anchor themselves in position to facilitate feeding and avoid being ejected by gut peristalsis. As they begin to feed on blood, juvenile worms mature into sexually dioecious adult parasites. Mature adult male and female hookworms mate, and female hookworms produce as many as 10,000 eggs per day. Eggs are evacuated from the host via the fecal stream. The process from L3 invasion to patency (egg production) takes approximately 6–8 weeks for *Necator americanus* and possibly a similar period of time for *Ancylostoma duodenale.* (Reproduced with permission from Loukas et al. [355]. © Springer Nature 2016)

and Prevention (CDC)'s Division of Parasitic Diseases and Malaria (DPDM) serves as a national reference laboratory for diagnosis of parasitic infection in the United States. A list of diagnostic procedures and specimen handling requirements can be found on their website (https://www.cdc.gov/dpdx/diagnosticprocedures/index.html).

For patients with severe, persistent, or atypical respiratory symptoms, or in immune-compromised individuals, bronchoscopy may be useful. Demonstration of peripheral or pulmonary eosinophilia, or elevated IgE, in the right epidemiological context, can be suggestive of parasitic infection. The following sections highlight the utility of vari-

Table 9.3 Helminth infections with pulmonary manifestations

Helminth	Mechanism of pulmonary involvement	Notable features of disease	Diagnosis
Ascaris lumbricoides	Hematogenous spread; inhalation/ aspiration	Associated with pulmonary eosinophilia and Loeffler syndrome Rarely, adult worms in the intestine can ascend into the oropharynx and cause airway obstruction	Detection of eggs in stool by light microscopy is primary means of diagnosis Serology available Adult worms may be directly visualized if coughed up or causing airway obstruction
Dirofilaria immitis	Hematogenous spread	Cause of canine heartworms Transmitted by mosquitoes *D. immitis* is a causative agent of human pulmonary dirofilariasis Symptomatic infection in humans is very rare Usually presents as an asymptomatic, solitary, well-circumscribed, peripheral nodule without calcification ("coin lesion") on imaging	Histology of biopsied tissue Serologic and molecular testing (PCR) available
Echinococcus species	Hematogenous or lymphatic spread; rarely via inhalation	Also known as hydatid disease Cystic echinococcus is the most common form of disease Symptoms develop when pulmonary cysts compress bronchi or rupture causing a hypersensitivity reaction Cysts are most often unilateral and solitary	Chest imaging (x-ray, CT scan, MRI) in conjunction with epidemiologic exposure Serologic tests available Bronchoscopy limited since rupture of cysts can induce hypersensitivity response; biopsy of cyst membrane may aid in diagnosis
Filariasis [*Brugia malayi, Wuchereria bancrofti*]	Hematogenous or lymphatic spread; immune-mediated inflammatory response	Adult worms in the lymphatics can release microfilariae into the systemic circulation, which can get trapped in the pulmonary circulation/lungs Associated with pulmonary and peripheral eosinophilia; may be referred to as tropical pulmonary eosinophilia May present as cough (often nocturnal) and dyspnea Peripheral signs of filariasis (lymphedema) may be present	Serologic tests used most often Filarial antigen may be present in blood Microfilariae can be visualized in blood or urine
Hookworms (*Necator americanus, Ancylostoma duodenale*)	Hematogenous spread	Enter body via percutaneous penetration from soil Organisms exit the vasculature via the alveolar capillaries and ascend into the GI tract Associated with pulmonary and peripheral eosinophilia during migratory phase Moderate or heavy intestinal infection associated with iron-deficiency anemia and hypoalbuminemia	Microscopic or molecular-based tests of stool Bronchoscopy could be used to detect larvae migrating from bronchi to trachea, but rarely performed

(continued)

Table 9.3 (continued)

Helminth	Mechanism of pulmonary involvement	Notable features of disease	Diagnosis
Lophomonas blattarum	Direct tissue infection	Rare protozoa carried by cockroaches and termites Vast majority of cases reported from China	Identification of flagellated organism from respiratory secretions (bronchoalveolar lavage fluid)
Paragonimus species	Direct migration from GI tract or liver to pleural cavity	Human infection from consumption of under- or uncooked shellfish (crabs or crayfish) May cause eosinophilic, chylous, or cholesterol pleural effusions Pleural (chest pain, dyspnea) and pulmonary symptoms (cough, hemoptysis) are most common clinical manifestation of infection Peripheral eosinophilia very common	Serology most commonly used Direct visualization of eggs in sputum (most often), but also BAL fluid, pleural fluid, biopsied tissue PCR available
Schistosoma species	Hematogenous spread; immune-mediated inflammatory response	Acquired via percutaneous penetration Pulmonary symptoms the result of a systemic hypersensitivity reaction during migration (first weeks after acquisition) Symptomatic infection more common in nonimmune individuals (i.e., travelers) Chronic pulmonary disease can result from egg deposition incidentally carried via venous system to pulmonary tissues; granulomas formation around eggs can lead to pulmonary hypertension	Demonstration of eggs in stool or urine by microscopy is primary means of diagnosis; lower sensitivity in acute infection since testing may be performed before eggs are deposited Serologic tests available; more useful in acute infection among individuals at low risk for past infection (i.e., travelers); not useful in endemic locations Bronchoscopy has limited role due to low organism burden within airways
Strongyloides stercoralis	Intestinal penetration and migration to lungs	Infection is mild in immune-competent individuals Disseminated infection (hyperinfection syndrome) can develop among immune-compromised patients, particularly those receiving steroids Associated with pulmonary eosinophilia	Stool microscopy is primary means of detection Serology available and useful in screening transplant candidates at high risk for hyperinfection syndrome Bronchoalveolar lavage may reveal larval forms in hyperinfection syndrome
Toxocara canis, Toxocara cati	Hematogenous spread	Larvae penetrate host tissues, including lung, and induce tissue-specific eosinophilia Peripheral eosinophilia common Pulmonary involvement associated with cough and wheeze	Serology is a preferred method of diagnosis Eosinophilia and elevated IgE common Peripheral nodular lung opacities may be present on imaging Pulmonary eosinophilia may be detected via bronchoscopy but direct detection of organism very rare

ous laboratory methods for diagnosing parasitic infections of the lung via bronchoscopy.

Culture

Very few parasites are diagnosed clinically using culture systems. For a number of reasons (low organism burden, varying life cycle, long replication half-life), it is difficult to grow parasites from human specimens in the laboratory. Thus, for the most part, parasite cultures are limited to research settings. While certain techniques have been developed to isolate organisms for antimicrobial susceptibility testing purposes [376], these are not used routinely in the clinical setting. As a result, parasite cultures are not generally performed on specimens obtained bronchoscopically.

PCR/Nucleic Acid Testing

Molecular diagnostic techniques are useful for the diagnosis of many parasitic infections and may be replacing conventional, microscopic approaches, especially for protozoa. Although sensitivity is variable, PCR tests are highly specific, often to the species level [377], and serve as good confirmatory tests [377–379]. PCR can also be performed on a variety of clinical specimens. Most often, parasitic infections are diagnosed via testing on blood/serum [378–381] and stool [382, 383]. In patients with suspected pulmonary infections, however, PCR can detect localized infection when performed on lung tissue or abscess fluid, such as for *Entamoeba histolytica* [383–385], *Echinococcus* spp. [386], and dirofilaria [387]. PCR also can detect the presence of various pathogens on BAL fluid, including schistosomiasis [388], *Toxoplasma gondii* [338, 389], and microsporidia [390]. However, due to the low organism burden associated with most parasitic infections involving the lung and lack of validation of many parasite PCRs from respiratory tract specimens, some experts debate PCR's utility over conventional staining techniques [391].

PCR from sputum holds potential to be a non-invasive method of detection of malaria, even though DNA in sputum may be several hundred-fold lower than that in blood [380]. In a study of 327 febrile individuals from India, 187 were diagnosed with malaria via microscopic evaluation [380]. The investigators found that a nested PCR assay of sputum identified more than 87% of microscopically confirmed cases [380].

Antigen-Based Testing

Direct fluorescent-antibody (DFA), enzyme immunoassays (EIA), and immunofluorescence assays (IFA) have been used for diagnosis of a limited number of protozoa including *Cryptosporidium* and *Giardia* species [382] and *Entamoeba histolytica* [383]. Commercially available assays are available, are more sensitive than direct microscopy, and have been incorporated into many clinical laboratories [383]. However, their use from BAL fluid or lung tissue is limited.

Pathology/Cytology

Light microscopy is the primary means of diagnosing the majority of parasitic infections [332, 364, 383]. Although sensitivity and specificity of microscopy is highly dependent on the technical skill of the microscopist, it is gold standard diagnostic method in parasitology. For parasitic gastrointestinal infections, direct wet-mount preparation is used for microscopic examination of stool ova and parasite (O & P) samples, while concentration and staining techniques increase the visualization of eggs, larvae, and cysts in samples [382, 383]. Direct visualization of eggs or adult worms from stool is specific, but sensitivity varies based on organism burden in intestinal lumen. Sampling of multiple stool specimens increases the likelihood of detection [364]. Kato-Katz thick smear is recommended by the World Health Organization for identification of soil-transmitted helminth infections such as *Ascaris lumbricoides*, *Trichuris trichiura,* and hookworms, as well as *Schistosoma* species [392]. Microscopic examination of Giemsa-stained blood films is the conventional approach

for diagnosis of bloodstream parasites such as in malaria and babesiosis. Indirect fluorescent antibody techniques are also available for a variety of parasitic species from tissue specimens.

Histopathology is particularly useful for diagnosing parasitic infections of the lung. Depending on the life cycle and migratory pattern of the parasite, eggs, larvae, or adult organisms may be detected in sputum samples, BAL fluid, or lung biopsy specimens [384]. Microscopic examination of sputum can be used to identify eggs of *Paragonimus westermani* [393] or larvae of *Strongyloides stercoralis* [394–396]; more rarely, larvae of *Ascaris lumbricoides*, hookworms, and *Entamoeba histolytica* can be detected in sputum. *Paragonimus* eggs can also be identified in pleural fluid on H&E stain, while adult flukes can be visualized within cystic cavities [384]. *Entamoeba histolytica* lung abscesses and empyemas may contain trophozoites that can be visualized on hematoxylin and eosin (H&E) or periodic acid Schiff (PAS) stains [384, 397]. *Schistosoma* spp. eggs and *Dirofilaria immitis* worms elicit granulomatous inflammation and necrosis, respectively, and can be directly visualized within biopsied lung tissue [384, 398]. Echinococcal cysts also have characteristic pathologic features that can be amenable to diagnosis via fiberoptic bronchoscopy [368, 384, 399, 400]. In rare cases of filariasis, microfilariae can be visualized on examination of bronchial lavage fluid [401, 402].

Airway Microbiome

In the past 15 years, molecular strategies have emerged for diagnosing bacterial and fungal infections that are less targeted. Whereas the molecular strategies discussed above target specific pathogens, new culture-independent techniques take an approach more akin to culture, in that they cast a wide net for many potential microorganisms, and then use modern DNA sequencing techniques to identify potential pathogens. Culture-independent techniques have so far mostly relied on the specific amplification of bacterial or fungal genes from BAL samples. In order to cast a wide net, the target genes need to be conserved across multiple species, such that they can be amplified with a common set of PCR primers, but they must be distinctive enough to allow identification (classification) to the species level. The most commonly used target for bacteria is the gene that encodes the small subunit of the ribosomal RNA (16S rRNA gene). For fungi, the corresponding small subunit, 18S, does not have enough discriminatory power, and the internal transcribed spacer (ITS) between the small and large subunit ribosomal RNA genes is often used.

Direct amplification and sequencing of the bacterial 16S rRNA genes from BAL fluid offers the potential for more sensitive detection of potential pathogens as compared to conventional bacterial cultures, but it also offers the possibility of collecting information on multiple microbial species and their relative abundances at once, opening up the prospect of understanding the ecology of infection and colonization [58, 403–406]. This new capability has led to two kinds of diagnostic goals: (1) finding the pathogen or pathogens without culture, and (2) illuminating properties of the full microbial community that may be biomarkers or even the root cause of disease. This second goal has taken microbiology out of the field of infectious diseases and placed it in allergy/immunology, rheumatology, and other pulmonary diseases.

Only a handful studies have used BAL to examine the pediatric microbiota in disease states such as protracted bacterial bronchitis [407], cystic fibrosis [58, 80, 408, 409], and patients with other chronic lung disease or immunocompromise [58, 406]. In general, these studies have demonstrated a diverse microbiota and, similar to studies done in adults [405], a high sensitivity for detecting bacteria in the lower respiratory tract [58]. Several studies [406, 410–412], but not all [58], have identified specific microbial community profiles associated with certain diseases or disease categories. However, the increased sensitivity of this technique also comes with a new diagnostic challenge. Samples often yield lists of more than 15 bacteria, and the most abundant bacteria are not always the pathogens recovered on standard culture from the same samples [58]. A detailed understanding of the relationship

between relative abundance, overall abundance, and microbial composition will be needed to make this technique clinically viable.

Another important question is whether or not invasive bronchoscopy with lavage is required to obtain the necessary information about the lower respiratory microbiota. Several studies have compared the microbiota of the upper and lower respiratory tract and reported varying levels of congruence and overlap in these microbial assemblages [67, 406, 413–420]. More work on paired upper and lower respiratory samples, in different age groups and types of disease, will be needed to resolve this issue.

Most respiratory microbiota (or microbiome) studies have been done targeting the 16S rRNA gene, and therefore, they can only detect bacteria and archaea. Several studies have used BAL other studies targeting fungi [421–430].

Fewer studies have analyzed BAL fluid for viruses [422, 431–434], but several studies aimed at viruses have been done on other respiratory samples (reviewed in [435]), some from pediatric populations [436–440]. Because viruses can have either RNA or DNA as their genetic material and do not have a single conserved gene among them, shot-gun metagenomic techniques, in which all nucleic acids in a sample are sequenced, remain the only option. Thus, studying the virome usually requires isolating viral sequences from a sea of human and microbial sequence data. However, studies that use a metagenomic approach also hold the promise of a complete picture of the respiratory microbiome. Such techniques are still costly and remain untested in the clinical setting.

References

1. Chellapandian D, Lehrnbecher T, Phillips B, Fisher BT, Zaoutis TE, Steinbach WJ, et al. Bronchoalveolar lavage and lung biopsy in patients with cancer and hematopoietic stem-cell transplantation recipients: a systematic review and meta-analysis. J Clin Oncol. 2015;33(5):501–9.
2. Efrati O, Sadeh-Gornik U, Modan-Moses D, Barak A, Szeinberg A, Vardi A, et al. Flexible bronchoscopy and bronchoalveolar lavage in pediatric patients with lung disease. Pediatr Crit Care Med. 2009;10(1):80–4.
3. Marchetti O, Lamoth F, Mikulska M, Viscoli C, Verweij P, Bretagne S, et al. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. Bone Marrow Transplant. 2012;47(6):846–54.
4. Lehrnbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol. 2017;35(18):2082–94.
5. Batra S, Li B, Underhill N, Maloney R, Katz BZ, Hijiya N. Clinical utility of bronchoalveolar lavage and respiratory tract biopsies in diagnosis and management of suspected invasive respiratory fungal infections in children. Pediatr Blood Cancer. 2015;62(9):1579–86.
6. Qualter E, Satwani P, Ricci A, Jin Z, Geyer MB, Alobeid B, et al. A comparison of bronchoalveolar lavage versus lung biopsy in pediatric recipients after stem cell transplantation. Biol Blood Marrow Transplant. 2014;20(8):1229–37.
7. Kottmann RM, Kelly J, Lyda E, Gurell M, Stalica J, Ormsby W, et al. Bronchoscopy with bronchoalveolar lavage: determinants of yield and impact on management in immunosuppressed patients. Thorax. 2011;66(9):823.
8. Nadimpalli S, Foca M, Satwani P, Sulis ML, Constantinescu A, Saiman L. Diagnostic yield of bronchoalveolar lavage in immunocompromised children with malignant and non-malignant disorders. Pediatr Pulmonol. 2017;52(6):820–6.
9. Peikert T, Rana S, Edell ES. Safety, diagnostic yield, and therapeutic implications of flexible bronchoscopy in patients with febrile neutropenia and pulmonary infiltrates. Mayo Clin Proc. 2005;80(11):1414–20.
10. Pagano L, Pagliari G, Basso A, Marra R, Sica S, Frigieri L, et al. The role of bronchoalveolar lavage in the microbiological diagnosis of pneumonia in patients with haematological malignancies. Ann Med. 1997;29(6):535–40.
11. Stokes DC, Shenep JL, Parham D, Bozeman PM, Marienchek W, Mackert PW. Role of flexible bronchoscopy in the diagnosis of pulmonary infiltrates in pediatric patients with cancer. J Pediatr. 1989;115(4):561–7.
12. Park JR, Fogarty S, Brogan TV. Clinical utility of bronchoalveolar lavage in pediatric cancer patients. Med Pediatr Oncol. 2002;39(3):175–80.
13. Rao U, Piccin A, Malone A, O'Hanlon K, Breatnach F, O'Meara A, et al. Utility of bronchoalveolar lavage in the diagnosis of pulmonary infection in children with haematological malignancies. Ir J Med Sci. 2013;182(2):177–83.
14. Carrillo-Marquez MA, Hulten KG, Hammerman W, Lamberth L, Mason EO, Kaplan SL. Staphylococcus aureus pneumonia in children in the era of community-acquired methicillin-resistance at

Texas Children's Hospital. Pediatr Infect Dis J. 2011;30(7):545–50.
15. Frush JM, Zhu Y, Edwards KM, Grijalva CG, Thomsen IP, Self WH, et al. Prevalence of Staphylococcus aureus and Use of Antistaphylococcal Therapy in Children Hospitalized with Pneumonia. J Hosp Med. 2018;13(12):848–52.
16. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372(9):835–45.
17. De Schutter I, De Wachter E, Crokaert F, Verhaegen J, Soetens O, Pierard D, et al. Microbiology of bronchoalveolar lavage fluid in children with acute nonresponding or recurrent community-acquired pneumonia: identification of nontypeable Haemophilus influenzae as a major pathogen. Clin Infect Dis. 2011;52(12):1437–44.
18. Shah SS, Dugan MH, Bell LM, Grundmeier RW, Florin TA, Hines EM, et al. Blood cultures in the emergency department evaluation of childhood pneumonia. Pediatr Infect Dis J. 2011;30(6):475–9.
19. Neuman MI, Hall M, Lipsett SC, Hersh AL, Williams DJ, Gerber JS, et al. Utility of Blood Culture Among Children Hospitalized With Community-Acquired Pneumonia. Pediatrics. 2017;140(3):e20171013.
20. Hickey RW, Bowman MJ, Smith GA. Utility of blood cultures in pediatric patients found to have pneumonia in the emergency department. Ann Emerg Med. 1996;27(6):721–5.
21. Bonadio WA. Bacteremia in febrile children with lobar pneumonia and leukocytosis. Pediatr Emerg Care. 1988;4(4):241–2.
22. Myers AL, Hall M, Williams DJ, Auger K, Tieder JS, Statile A, et al. Prevalence of bacteremia in hospitalized pediatric patients with community-acquired pneumonia. Pediatr Infect Dis J. 2013;32(7):736–40.
23. Byington CL, Spencer LY, Johnson TA, Pavia AT, Allen D, Mason EO, et al. An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations. Clin Infect Dis. 2002;34(4):434–40.
24. Waterer GW, Wunderink RG. The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. Respir Med. 2001;95(1):78–82.
25. Picard E, Joseph L, Goldberg S, Mimouni FB, Deeb M, Kleid D, et al. Predictive factors of morbidity in childhood parapneumonic effusion-associated pneumonia: a retrospective study. Pediatr Infect Dis J. 2010;29(9):840–3.
26. Freij BJ, Kusmiesz H, Nelson JD, McCracken GH Jr. Parapneumonic effusions and empyema in hospitalized children: a retrospective review of 227 cases. Pediatr Infect Dis. 1984;3(6):578–91.
27. Hoff SJ, Neblett WW, Edwards KM, Heller RM, Pietsch JB, Holcomb GW Jr, et al. Parapneumonic empyema in children: decortication hastens recovery in patients with severe pleural infections. Pediatr Infect Dis J. 1991;10(3):194–9.
28. Loens K, Van Heirstraeten L, Malhotra-Kumar S, Goossens H, Ieven M. Optimal sampling sites and methods for detection of pathogens possibly causing community-acquired lower respiratory tract infections. J Clin Microbiol. 2009;47(1):21–31.
29. Heiskanen-Kosma T, Korppi M, Jokinen C, Kurki S, Heiskanen L, Juvonen H, et al. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. Pediatr Infect Dis J. 1998;17(11):986–91.
30. McCracken GH Jr. Etiology and treatment of pneumonia. Pediatr Infect Dis J. 2000;19(4):373–7.
31. Tsolia MN, Psarras S, Bossios A, Audi H, Paldanius M, Gourgiotis D, et al. Etiology of community-acquired pneumonia in hospitalized school-age children: evidence for high prevalence of viral infections. Clin Infect Dis. 2004;39(5):681–6.
32. Xu D, Li S, Chen Z, Du L. Detection of Mycoplasma pneumoniae in different respiratory specimens. Eur J Pediatr. 2011;170(7):851–8.
33. Parides GC, Bloom JW, Ampel NM, Ray CG. Mycoplasma and ureaplasma in bronchoalveolar lavage fluids from immunocompromised hosts. Diagn Microbiol Infect Dis. 1988;9(1):55–7.
34. Phin N, Parry-Ford F, Harrison T, Stagg HR, Zhang N, Kumar K, et al. Epidemiology and clinical management of Legionnaires' disease. Lancet Infect Dis. 2014;14(10):1011–21.
35. Pierre DM, Baron J, Yu VL, Stout JE. Diagnostic testing for Legionnaires' disease. Ann Clin Microbiol Antimicrob. 2017;16(1):59.
36. Mercante JW, Winchell JM. Current and emerging Legionella diagnostics for laboratory and outbreak investigations. Clin Microbiol Rev. 2015;28(1):95–133.
37. Venkatachalam V, Hendley JO, Willson DF. The diagnostic dilemma of ventilator-associated pneumonia in critically ill children. Pediatr Crit Care Med. 2011;12(3):286–96.
38. Srinivasan R, Asselin J, Gildengorin G, Wiener-Kronish J, Flori HR. A prospective study of ventilator-associated pneumonia in children. Pediatrics. 2009;123(4):1108–15.
39. Charles MP, Kali A, Easow JM, Joseph NM, Ravishankar M, Srinivasan S, et al. Ventilator-associated pneumonia. Australas Med J. 2014;7(8):334–44.
40. Robert R, Grollier G, Frat JP, Godet C, Adoun M, Fauchere JL, et al. Colonization of lower respiratory tract with anaerobic bacteria in mechanically ventilated patients. Intensive Care Med. 2003;29(7):1062–8.
41. Klompas M. Does this patient have ventilator-associated pneumonia? JAMA. 2007;297(14):1583–93.
42. Gauvin F, Dassa C, Chaibou M, Proulx F, Farrell CA, Lacroix J. Ventilator-associated pneumonia in intu-

bated children: comparison of different diagnostic methods. Pediatr Crit Care Med. 2003;4(4):437–43.
43. Chastre J, Fagon JY, Bornet-Lecso M, Calvat S, Dombret MC, al Khani R, et al. Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med. 1995;152(1):231–40.
44. Fabregas N, Ewig S, Torres A, El-Ebiary M, Ramirez J, de La Bellacasa JP, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. Thorax. 1999;54(10):867–73.
45. Torres A, Fabregas N, Ewig S, de la Bellacasa JP, Bauer TT, Ramirez J. Sampling methods for ventilator-associated pneumonia: validation using different histologic and microbiological references. Crit Care Med. 2000;28(8):2799–804.
46. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med. 2000;132(8):621–30.
47. Shorr AF, Sherner JH, Jackson WL, Kollef MH. Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. Crit Care Med. 2005;33(1):46–53.
48. Canadian Critical Care Trials G. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med. 2006;355(25):2619–30.
49. Wood AY, Davit AJ 2nd, Ciraulo DL, Arp NW, Richart CM, Maxwell RA, et al. A prospective assessment of diagnostic efficacy of blind protective bronchial brushings compared to bronchoscope-assisted lavage, bronchoscope-directed brushings, and blind endotracheal aspirates in ventilator-associated pneumonia. J Trauma. 2003;55(5):825–34.
50. Labenne M, Poyart C, Rambaud C, Goldfarb B, Pron B, Jouvet P, et al. Blind protected specimen brush and bronchoalveolar lavage in ventilated children. Crit Care Med. 1999;27(11):2537–43.
51. Gauvin F, Lacroix J, Guertin MC, Proulx F, Farrell CA, Moghrabi A, et al. Reproducibility of blind protected bronchoalveolar lavage in mechanically ventilated children. Am J Respir Crit Care Med. 2002;165(12):1618–23.
52. Zucker A, Pollack M, Katz R. Blind use of the double-lumen plugged catheter for diagnosis of respiratory tract infections in critically ill children. Crit Care Med. 1984;12(10):867–70.
53. Sachdev A, Chugh K, Raghunathan V, Gupta D, Wattal C, Menon GR. Diagnosis of bacterial ventilator-associated pneumonia in children: reproducibility of blind bronchial sampling. Pediatr Crit Care Med. 2013;14(1):e1–7.
54. Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D, et al. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: diagnosis and treatment. J Crit Care. 2008;23(1):138–47.
55. Sachdev A, Chugh K, Sethi M, Gupta D, Wattal C, Menon G. Diagnosis of ventilator-associated pneumonia in children in resource-limited setting: a comparative study of bronchoscopic and non-bronchoscopic methods. Pediatr Crit Care Med. 2010;11(2):258–66.
56. Morrow BM, Argent AC, Jeena PM, Green RJ. Guideline for the diagnosis, prevention and treatment of paediatric ventilator-associated pneumonia. S Afr Med J. 2009;99(4 Pt 2):255–67.
57. Rizik S, Hakim F, Bentur L, Arad-Cohen N, Kassis I. Bronchoscopy and bronchoalveolar lavage in the diagnosis and management of pulmonary infections in immunocompromised children. J Pediatr Hematol Oncol. 2018;40(7):532–5.
58. Zachariah P, Ryan C, Nadimpalli S, Coscia G, Kolb M, Smith H, et al. Culture-independent analysis of pediatric bronchoalveolar lavage specimens. Ann Am Thorac Soc. 2018;15(9):1047–56.
59. Muhlebach MS, Hatch JE, Einarsson GG, McGrath SJ, Gilipin DF, Lavelle G, et al. Anaerobic bacteria cultured from cystic fibrosis airways correlate to milder disease: a multisite study. Eur Respir J. 2018;52(1):1800242.
60. Sherrard LJ, Bell SC, Tunney MM. The role of anaerobic bacteria in the cystic fibrosis airway. Curr Opin Pulm Med. 2016;22(6):637–43.
61. Tunney MM, Field TR, Moriarty TF, Patrick S, Doering G, Muhlebach MS, et al. Detection of anaerobic bacteria in high numbers in sputum from patients with cystic fibrosis. Am J Respir Crit Care Med. 2008;177(9):995–1001.
62. Foundation CF. Patient registry annual report. Bethesda, Maryland; 2017.
63. Chung JC, Becq J, Fraser L, Schulz-Trieglaff O, Bond NJ, Foweraker J, et al. Genomic variation among contemporary Pseudomonas aeruginosa isolates from chronically infected cystic fibrosis patients. J Bacteriol. 2012;194(18):4857–66.
64. Foweraker JE, Laughton CR, Brown DF, Bilton D. Phenotypic variability of Pseudomonas aeruginosa in sputa from patients with acute infective exacerbation of cystic fibrosis and its impact on the validity of antimicrobial susceptibility testing. J Antimicrob Chemother. 2005;55(6):921–7.
65. Winstanley C, O'Brien S, Brockhurst MA. Pseudomonas aeruginosa evolutionary adaptation and diversification in cystic fibrosis chronic lung infections. Trends Microbiol. 2016;24(5):327–37.
66. Jorth P, Staudinger BJ, Wu X, Hisert KB, Hayden H, Garudathri J, et al. Regional isolation drives bacterial diversification within cystic fibrosis lungs. Cell Host Microbe. 2015;18(3):307–19.
67. Goddard AF, Staudinger BJ, Dowd SE, Joshi-Datar A, Wolcott RD, Aitken ML, et al. Direct sampling of cystic fibrosis lungs indicates that DNA-based analyses of upper-airway specimens can misrepresent lung microbiota. Proc Natl Acad Sci U S A. 2012;109(34):13769–74.

68. Willner D, Haynes MR, Furlan M, Hanson N, Kirby B, Lim YW, et al. Case studies of the spatial heterogeneity of DNA viruses in the cystic fibrosis lung. Am J Respir Cell Mol Biol. 2012;46(2):127–31.
69. Willner D, Haynes MR, Furlan M, Schmieder R, Lim YW, Rainey PB, et al. Spatial distribution of microbial communities in the cystic fibrosis lung. ISME J. 2012;6(2):471–4.
70. Eyns H, Pierard D, De Wachter E, Eeckhout L, Vaes P, Malfroot A. Respiratory bacterial culture sampling in expectorating and non-expectorating patients with cystic fibrosis. Front Pediatr. 2018;6:403.
71. Ramsey BW, Wentz KR, Smith AL, Richardson M, Williams-Warren J, Hedges DL, et al. Predictive value of oropharyngeal cultures for identifying lower airway bacteria in cystic fibrosis patients. Am Rev Respir Dis. 1991;144(2):331–7.
72. Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phelan PD. Bronchoalveolar lavage or oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. Pediatr Pulmonol. 1996;21(5):267–75.
73. Burns JL, Gibson RL, McNamara S, Yim D, Emerson J, Rosenfeld M, et al. Longitudinal assessment of Pseudomonas aeruginosa in young children with cystic fibrosis. J Infect Dis. 2001;183(3):444–52.
74. Equi AC, Pike SE, Davies J, Bush A. Use of cough swabs in a cystic fibrosis clinic. Arch Dis Child. 2001;85(5):438–9.
75. Rosenfeld M, Emerson J, Accurso F, Armstrong D, Castile R, Grimwood K, et al. Diagnostic accuracy of oropharyngeal cultures in infants and young children with cystic fibrosis. Pediatr Pulmonol. 1999;28(5):321–8.
76. Jung A, Kleinau I, Schonian G, Bauernfeind A, Chen C, Griese M, et al. Sequential genotyping of Pseudomonas aeruginosa from upper and lower airways of cystic fibrosis patients. Eur Respir J. 2002;20(6):1457–63.
77. Doumit M, Belessis Y, Stelzer-Braid S, Mallitt KA, Rawlinson W, Jaffe A. Diagnostic accuracy and distress associated with oropharyngeal suction in cystic fibrosis. J Cyst Fibros. 2016;15(4):473–8.
78. Aaron SD, Kottachchi D, Ferris WJ, Vandemheen KL, St Denis ML, Plouffe A, et al. Sputum versus bronchoscopy for diagnosis of Pseudomonas aeruginosa biofilms in cystic fibrosis. Eur Respir J. 2004;24(4):631–7.
79. Jain K, Wainwright C, Smyth AR. Bronchoscopy-guided antimicrobial therapy for cystic fibrosis. Cochrane Database Syst Rev. 2018;9:CD009530.
80. Laguna TA, Wagner BD, Williams CB, Stevens MJ, Robertson CE, Welchlin CW, et al. Airway microbiota in bronchoalveolar lavage fluid from clinically well infants with cystic fibrosis. PLoS One. 2016;11(12):e0167649.
81. Hogan DA, Willger SD, Dolben EL, Hampton TH, Stanton BA, Morrison HG, et al. Analysis of lung microbiota in bronchoalveolar lavage, protected brush and sputum samples from subjects with mild-to-moderate cystic fibrosis lung disease. PLoS One. 2016;11(3):e0149998.
82. Hoppe JE, Towler E, Wagner BD, Accurso FJ, Sagel SD, Zemanick ET. Sputum induction improves detection of pathogens in children with cystic fibrosis. Pediatr Pulmonol. 2015;50(7):638–46.
83. Suri R, Marshall LJ, Wallis C, Metcalfe C, Shute JK, Bush A. Safety and use of sputum induction in children with cystic fibrosis. Pediatr Pulmonol. 2003;35(4):309–13.
84. Al-Saleh S, Dell SD, Grasemann H, Yau YC, Waters V, Martin S, et al. Sputum induction in routine clinical care of children with cystic fibrosis. J Pediatr. 2010;157(6):1006–11 e1.
85. Ho SA, Ball R, Morrison LJ, Brownlee KG, Conway SP. Clinical value of obtaining sputum and cough swab samples following inhaled hypertonic saline in children with cystic fibrosis. Pediatr Pulmonol. 2004;38(1):82–7.
86. Mussaffi H, Fireman EM, Mei-Zahav M, Prais D, Blau H. Induced sputum in the very young: a new key to infection and inflammation. Chest. 2008;133(1):176–82.
87. Henig NR, Tonelli MR, Pier MV, Burns JL, Aitken ML. Sputum induction as a research tool for sampling the airways of subjects with cystic fibrosis. Thorax. 2001;56(4):306–11.
88. Angrill J, Agusti C, de Celis R, Rano A, Gonzalez J, Sole T, et al. Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. Thorax. 2002;57(1):15–9.
89. Ronchetti K, Tame JD, Paisey C, Thia LP, Doull I, Howe R, et al. The CF-Sputum Induction Trial (CF-SpIT) to assess lower airway bacterial sampling in young children with cystic fibrosis: a prospective internally controlled interventional trial. Lancet Respir Med. 2018;6(6):461–71.
90. Blau H, Linnane B, Carzino R, Tannenbaum EL, Skoric B, Robinson PJ, et al. Induced sputum compared to bronchoalveolar lavage in young, non-expectorating cystic fibrosis children. J Cyst Fibros. 2014;13(1):106–10.
91. O'Horo JC, Thompson D, Safdar N. Is the gram stain useful in the microbiologic diagnosis of VAP? A meta-analysis. Clin Infect Dis. 2012;55(4):551–61.
92. Meduri GU, Baselski V. The role of bronchoalveolar lavage in diagnosing nonopportunistic bacterial pneumonia. Chest. 1991;100(1):179–90.
93. de Blic J, Midulla F, Barbato A, Clement A, Dab I, Eber E, et al. Bronchoalveolar lavage in children. ERS Task Force on bronchoalveolar lavage in children. European Respiratory Society. Eur Respir J. 2000;15(1):217–31.
94. Jourdain B, Joly-Guillou ML, Dombret MC, Calvat S, Trouillet JL, Gibert C, et al. Usefulness of quantitative cultures of BAL fluid for diagnosing nosocomial pneumonia in ventilated patients. Chest. 1997;111(2):411–8.

95. Kirkpatrick MB, Bass JB Jr. Quantitative bacterial cultures of bronchoalveolar lavage fluids and protected brush catheter specimens from normal subjects. Am Rev Respir Dis. 1989;139(2):546–8.
96. Cantral DE, Tape TG, Reed EC, Spurzem JR, Rennard SI, Thompson AB. Quantitative culture of bronchoalveolar lavage fluid for the diagnosis of bacterial pneumonia. Am J Med. 1993;95(6):601–7.
97. Rasmussen TR, Korsgaard J, Moller JK, Sommer T, Kilian M. Quantitative culture of bronchoalveolar lavage fluid in community-acquired lower respiratory tract infections. Respir Med. 2001;95(11):885–90.
98. Thorpe JE, Baughman RP, Frame PT, Wesseler TA, Staneck JL. Bronchoalveolar lavage for diagnosing acute bacterial pneumonia. J Infect Dis. 1987;155(5):855–61.
99. Prats E, Dorca J, Pujol M, Garcia L, Barreiro B, Verdaguer R, et al. Effects of antibiotics on protected specimen brush sampling in ventilator-associated pneumonia. Eur Respir J. 2002;19(5):944–51.
100. Torres A, el-Ebiary M, Padro L, Gonzalez J, de la Bellacasa JP, Ramirez J, et al. Validation of different techniques for the diagnosis of ventilator-associated pneumonia. Comparison with immediate postmortem pulmonary biopsy. Am J Respir Crit Care Med. 1994;149(2 Pt 1):324–31.
101. Kim ES, Kim EC, Lee SM, Yang SC, Yoo CG, Kim YW, et al. Bacterial yield from quantitative cultures of bronchoalveolar lavage fluid in patients with pneumonia on antimicrobial therapy. Korean J Intern Med. 2012;27(2):156–62.
102. Torres A, Lee N, Cilloniz C, Vila J, Van der Eerden M. Laboratory diagnosis of pneumonia in the molecular age. Eur Respir J. 2016;48(6):1764–78.
103. Falguera M, Lopez A, Nogues A, Porcel JM, Rubio-Caballero M. Evaluation of the polymerase chain reaction method for detection of Streptococcus pneumoniae DNA in pleural fluid samples. Chest. 2002;122(6):2212–6.
104. Lahti E, Mertsola J, Kontiokari T, Eerola E, Ruuskanen O, Jalava J. Pneumolysin polymerase chain reaction for diagnosis of pneumococcal pneumonia and empyema in children. Eur J Clin Microbiol Infect Dis. 2006;25(12):783–9.
105. Krenke K, Sadowy E, Podsiadly E, Hryniewicz W, Demkow U, Kulus M. Etiology of parapneumonic effusion and pleural empyema in children. The role of conventional and molecular microbiological tests. Respir Med. 2016;116:28–33.
106. Le Monnier A, Carbonnelle E, Zahar JR, Le Bourgeois M, Abachin E, Quesne G, et al. Microbiological diagnosis of empyema in children: comparative evaluations by culture, polymerase chain reaction, and pneumococcal antigen detection in pleural fluids. Clin Infect Dis. 2006;42(8):1135–40.
107. Abdeldaim GM, Stralin K, Olcen P, Blomberg J, Herrmann B. Toward a quantitative DNA-based definition of pneumococcal pneumonia: a comparison of Streptococcus pneumoniae target genes, with special reference to the Spn9802 fragment. Diagn Microbiol Infect Dis. 2008;60(2):143–50.
108. Johansson N, Kalin M, Giske CG, Hedlund J. Quantitative detection of Streptococcus pneumoniae from sputum samples with real-time quantitative polymerase chain reaction for etiologic diagnosis of community-acquired pneumonia. Diagn Microbiol Infect Dis. 2008;60(3):255–61.
109. Menezes-Martins LF, Menezes-Martins JJ, Michaelsen VS, Aguiar BB, Ermel T, Machado DC. Diagnosis of parapneumonic pleural effusion by polymerase chain reaction in children. J Pediatr Surg. 2005;40(7):1106–10.
110. Abdeldaim GM, Stralin K, Olcen P, Blomberg J, Molling P, Herrmann B. Quantitative fucK gene polymerase chain reaction on sputum and nasopharyngeal secretions to detect Haemophilus influenzae pneumonia. Diagn Microbiol Infect Dis. 2013;76(2):141–6.
111. Abdeldaim GM, Herrmann B. PCR detection of Haemophilus influenzae from respiratory specimens. Methods Mol Biol. 2013;943:115–23.
112. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis. 2010;50(2):202–9.
113. Stralin K, Korsgaard J, Olcen P. Evaluation of a multiplex PCR for bacterial pathogens applied to bronchoalveolar lavage. Eur Respir J. 2006;28(3):568–75.
114. Xirogianni A, Tsolia M, Voyiatzi A, Sioumala M, Makri A, Argyropoulou A, et al. Diagnosis of upper and lower respiratory tract bacterial infections with the use of multiplex PCR assays. Diagnostics (Basel). 2013;3(2):222–31.
115. Sansot M, Fradin E, Chenouard R, Kempf M, Kouatchet A, Lasocki S, et al. Performance of the extended use of the FilmArray((R)) BCID panel kit for bronchoalveolar lavage analysis. Mol Biol Rep. 2019;46(3):2685–92.
116. Murdoch DR, Anderson TP, Beynon KA, Chua A, Fleming AM, Laing RT, et al. Evaluation of a PCR assay for detection of Streptococcus pneumoniae in respiratory and nonrespiratory samples from adults with community-acquired pneumonia. J Clin Microbiol. 2003;41(1):63–6.
117. Stralin K, Tornqvist E, Kaltoft MS, Olcen P, Holmberg H. Etiologic diagnosis of adult bacterial pneumonia by culture and PCR applied to respiratory tract samples. J Clin Microbiol. 2006;44(2):643–5.
118. Stralin K, Herrmann B, Abdeldaim G, Olcen P, Holmberg H, Molling P. Comparison of sputum and nasopharyngeal aspirate samples and of the PCR gene targets lytA and Spn9802 for quantitative PCR for rapid detection of pneumococcal pneumonia. J Clin Microbiol. 2014;52(1):83–9.
119. Carvalho Mda G, Tondella ML, McCaustland K, Weidlich L, McGee L, Mayer LW, et al. Evaluation and improvement of real-time PCR assays targeting lytA, ply, and psaA genes for detection of

pneumococcal DNA. J Clin Microbiol. 2007;45(8):2460–6.
120. Abdeldaim G, Herrmann B, Molling P, Holmberg H, Blomberg J, Olcen P, et al. Usefulness of real-time PCR for lytA, ply, and Spn9802 on plasma samples for the diagnosis of pneumococcal pneumonia. Clin Microbiol Infect. 2010;16(8):1135–41.
121. Albrich WC, Madhi SA, Adrian PV, Telles JN, Paranhos-Baccala G, Klugman KP. Genomic load from sputum samples and nasopharyngeal swabs for diagnosis of pneumococcal pneumonia in HIV-infected adults. J Clin Microbiol. 2014;52(12):4224–9.
122. Albrich WC, Madhi SA, Adrian PV, van Niekerk N, Mareletsi T, Cutland C, et al. Use of a rapid test of pneumococcal colonization density to diagnose pneumococcal pneumonia. Clin Infect Dis. 2012;54(5):601–9.
123. Lorente ML, Falguera M, Nogues A, Gonzalez AR, Merino MT, Caballero MR. Diagnosis of pneumococcal pneumonia by polymerase chain reaction (PCR) in whole blood: a prospective clinical study. Thorax. 2000;55(2):133–7.
124. Sheppard CL, Harrison TG, Kearns AM, Guiver M, Creek M, Evans R, et al. Diagnosis of invasive pneumococcal infection by PCR amplification of Streptococcus pneumoniae genomic fragments in blood: a multi-centre comparative study. Commun Dis Public Health. 2003;6(3):221–7.
125. Yang S, Lin S, Khalil A, Gaydos C, Nuemberger E, Juan G, et al. Quantitative PCR assay using sputum samples for rapid diagnosis of pneumococcal pneumonia in adult emergency department patients. J Clin Microbiol. 2005;43(7):3221–6.
126. Peters RP, de Boer RF, Schuurman T, Gierveld S, Kooistra-Smid M, van Agtmael MA, et al. Streptococcus pneumoniae DNA load in blood as a marker of infection in patients with community-acquired pneumonia. J Clin Microbiol. 2009;47(10):3308–12.
127. Smith MD, Sheppard CL, Hogan A, Harrison TG, Dance DA, Derrington P, et al. Diagnosis of Streptococcus pneumoniae infections in adults with bacteremia and community-acquired pneumonia: clinical comparison of pneumococcal PCR and urinary antigen detection. J Clin Microbiol. 2009;47(4):1046–9.
128. Gollomp K, Rankin SC, White C, Mattei P, Harris MC, Kilpatrick LE, et al. Broad-range bacterial polymerase chain reaction in the microbiologic diagnosis of complicated pneumonia. J Hosp Med. 2012;7(1):8–13.
129. Adjemian J, Olivier KN, Seitz AE, Falkinham JO, Holland SM, Prevots DR. Spatial clusters of nontuberculous mycobacterial lung disease in the United States. Am J Respir Crit Care Med. 2012;186(6):553–8.
130. Prevots DR, Shaw PA, Strickland D, Jackson LA, Raebel MA, Blosky MA, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. Am J Respir Crit Care Med. 2010;182(7):970–6.
131. Brode SK, Daley CL, Marras TK. The epidemiologic relationship between tuberculosis and nontuberculous mycobacterial disease: a systematic review. Int J Tuberc Lung Dis. 2014;18(11):1370–7.
132. Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. Am J Respir Crit Care Med. 2012;185(8):881–6.
133. Henkle E, Hedberg K, Schafer S, Novosad S, Winthrop KL. Population-based incidence of pulmonary nontuberculous mycobacterial disease in Oregon 2007 to 2012. Ann Am Thorac Soc. 2015;12(5):642–7.
134. Runyon EH. Anonymous mycobacteria in pulmonary disease. Med Clin North Am. 1959;43(1):273–90.
135. WHO. Global tuberculosis report. Geneva: World Health Organization; 2017.
136. Keshavjee S, Farmer PE. Tuberculosis, drug resistance, and the history of modern medicine. N Engl J Med. 2012;367(10):931–6.
137. Ellner J. Tuberculosis. In: Goldman L, Schafer AI, editors. Goldman's cecil medicine. 24th ed. New York: Elsevier; 2012. p. 1939–48.
138. American Academy of Pediatrics. Tuberculosis. In: Kimberlin D, Brady M, Jackson MA, Long S, editors. Red book. Elk Grove Village: American Academy of Pediatrics; 2018. p. 829–53.
139. Goussard P, Gie R. The role of bronchoscopy in the diagnosis and management of pediatric pulmonary tuberculosis. Expert Rev Respir Med. 2014;8(1):101–9.
140. Martiniano SL, Nick JA, Daley CL. Nontuberculous mycobacterial infections in cystic fibrosis. Clin Chest Med. 2016;37(1):83–96.
141. Faro A. Pulmonary disease in cystic fibrosis. In: Bush A, Wilmott R, Chernick V, Boat T, Ratjen F, Deterding R, editors. Kendig & Chernick's disorders of the respiratory tract in children. Philadelphia, PA: Elsevier; 2012. p. 770–80.
142. Ashbolt NJ. Environmental (Saprozoic) pathogens of engineered water systems: understanding their ecology for risk assessment and management. Pathogens. 2015;4(2):390–405.
143. Parkins MD, Floto RA. Emerging bacterial pathogens and changing concepts of bacterial pathogenesis in cystic fibrosis. J Cyst Fibros. 2015;14(3):293–304.
144. Ramsay KA, Stockwell RE, Bell SC, Kidd TJ. Infection in cystic fibrosis: impact of the environment and climate. Expert Rev Respir Med. 2016;10(5):505–19.
145. Whittaker LA, Teneback C. Atypical mycobacterial and fungal infections in cystic fibrosis. Semin Respir Crit Care Med. 2009;30(5):539–46.
146. Holland SM. The nontuberculous mycobacteria. In: Goldman L, Schafer AI, editors. Goldman's cecil medicine. New York: Elsevier; 2012. p. 1948–50.

147. Adjemian J, Olivier KN, Prevots DR. Nontuberculous mycobacteria among patients with cystic fibrosis in the United States: screening practices and environmental risk. Am J Respir Crit Care Med. 2014;190(5):581–6.
148. Adjemian J, Daniel-Wayman S, Ricotta E, Prevots DR. Epidemiology of nontuberculous mycobacteriosis. Semin Respir Crit Care Med. 2018;39(3):325–35.
149. Donohue MJ, Wymer L. Increasing prevalence rate of nontuberculous mycobacteria infections in five states, 2008-2013. Ann Am Thorac Soc. 2016;13(12):2143–50.
150. Hoefsloot W, van Ingen J, Andrejak C, Angeby K, Bauriaud R, Bemer P, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. Eur Respir J. 2013;42(6):1604–13.
151. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367–416.
152. Koh WJ. Nontuberculous mycobacteria-overview. Microbiol Spectr. 2017;5(1) https://doi.org/10.1128/microbiolspec.TNMI7-0024-2016.
153. Adjemian J, Alison MB, Kenneth NO, Prevots DR. Nontuberculous mycobacterial disease among cystic fibrosis patients in the United States: Environmental Risk and NTM Screening Practices. C17 CYSTIC FIBROSIS LUNG INFECTIONS. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2014. p. A3955-A.
154. Bar-On O, Mussaffi H, Mei-Zahav M, Prais D, Steuer G, Stafler P, et al. Increasing nontuberculous mycobacteria infection in cystic fibrosis. J Cyst Fibros. 2015;14(1):53–62.
155. Martiniano SL, Davidson RM, Nick JA. Nontuberculous mycobacteria in cystic fibrosis: updates and the path forward. Pediatr Pulmonol. 2017;52(S48):S29–36.
156. Binder AM, Adjemian J, Olivier KN, Prevots DR. Epidemiology of nontuberculous mycobacterial infections and associated chronic macrolide use among persons with cystic fibrosis. Am J Respir Crit Care Med. 2013;188(7):807–12.
157. Olivier KN, Weber DJ, Wallace RJ, Faiz AR, Lee JH, Zhang Y, et al. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med. 2003;167(6):828–34.
158. Smith MJ, Efthimiou J, Hodson ME, Batten JC. Mycobacterial isolations in young adults with cystic fibrosis. Thorax. 1984;39(5):369–75.
159. Raidt L, Idelevich EA, Dübbers A, Küster P, Drevinek P, Peters G, et al. Increased prevalence and resistance of important pathogens recovered from respiratory specimens of cystic fibrosis patients during a decade. Pediatr Infect Dis J. 2015;34(7):700–5.
160. Saiman L, Siegel JD, LiPuma JJ, Brown RF, Bryson EA, Chambers MJ, et al. Infection prevention and control guideline for cystic fibrosis: 2013 update. Infect Control Hosp Epidemiol. 2014;35(Suppl 1):S1–S67.
161. Olivier KN, Weber DJ, Lee JH, Handler A, Tudor G, Molina PL, et al. Nontuberculous mycobacteria. II: nested-cohort study of impact on cystic fibrosis lung disease. Am J Respir Crit Care Med. 2003;167(6):835–40.
162. Catherinot E, Roux AL, Vibet MA, Bellis G, Lemonnier L, Le Roux E, et al. Inhaled therapies, azithromycin and Mycobacterium abscessus in cystic fibrosis patients. Eur Respir J. 2013;41(5):1101–6.
163. Catherinot E, Roux AL, Vibet MA, Bellis G, Ravilly S, Lemonnier L, et al. Mycobacterium avium and Mycobacterium abscessus complex target distinct cystic fibrosis patient subpopulations. J Cyst Fibros. 2013;12(1):74–80.
164. Coolen N, Morand P, Martin C, Hubert D, Kanaan R, Chapron J, et al. Reduced risk of nontuberculous mycobacteria in cystic fibrosis adults receiving long-term azithromycin. J Cyst Fibros. 2015;14(5):594–9.
165. Leung JM, Olivier KN. Nontuberculous mycobacteria in patients with cystic fibrosis. Semin Respir Crit Care Med. 2013;34(1):124–34.
166. Verregghen M, Heijerman HG, Reijers M, van Ingen J, van der Ent CK. Risk factors for Mycobacterium abscessus infection in cystic fibrosis patients; a case-control study. J Cyst Fibros. 2012;11(4):340–3.
167. Viviani L, Harrison MJ, Zolin A, Haworth CS, Floto RA. Epidemiology of nontuberculous mycobacteria (NTM) amongst individuals with cystic fibrosis (CF). J Cyst Fibros. 2016;15(5):619–23.
168. Girón RM, Máiz L, Barrio I, Martínez MT, Salcedo A, Prados C. Nontuberculous mycobacterial infection in patients with cystic fibrosis: a multicenter prevalence study. Arch Bronconeumol. 2008;44(12):679–84.
169. Levy I, Grisaru-Soen G, Lerner-Geva L, Kerem E, Blau H, Bentur L, et al. Multicenter cross-sectional study of nontuberculous mycobacterial infections among cystic fibrosis patients, Israel. Emerg Infect Dis. 2008;14(3):378–84.
170. Radhakrishnan DK, Yau Y, Corey M, Richardson S, Chedore P, Jamieson F, et al. Non-tuberculous mycobacteria in children with cystic fibrosis: isolation, prevalence, and predictors. Pediatr Pulmonol. 2009;44(11):1100–6.
171. Jennifer A, Alison MB, Kenneth NO, Prevots DR. Nontuberculous mycobacterial disease among cystic fibrosis patients in the United States: Environmental Risk and NTM Screening Practices. C17 Cystic Fibrosis Lung Infections. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2014. p. A3955-A.
172. Jennifer A, Kenneth NO, Prevots DR. Predictors of prolonged nontuberculous mycobacterial infections in patients with cystic fibrosis. C105 Nontuberculous Mycobacteria Epidemiology. American Thoracic Society International Conference Abstracts: American Thoracic Society; 2015. p. A5255-A.

173. Mussaffi H, Rivlin J, Shalit I, Ephros M, Blau H. Nontuberculous mycobacteria in cystic fibrosis associated with allergic bronchopulmonary aspergillosis and steroid therapy. Eur Respir J. 2005;25(2):324–8.
174. Sermet-Gaudelus I, Le Bourgeois M, Pierre-Audigier C, Offredo C, Guillemot D, Halley S, et al. Mycobacterium abscessus and children with cystic fibrosis. Emerg Infect Dis. 2003;9(12):1587–91.
175. Bouso JM, Burns JJ, Amin R, Livingston FR, Elidemir O. Household proximity to water and nontuberculous mycobacteria in children with cystic fibrosis. Pediatr Pulmonol. 2017;52(3):324–30.
176. Bryant JM, Grogono DM, Greaves D, Foweraker J, Roddick I, Inns T, et al. Whole-genome sequencing to identify transmission of Mycobacterium abscessus between patients with cystic fibrosis: a retrospective cohort study. Lancet. 2013;381(9877):1551–60.
177. Harris KA, Underwood A, Kenna DT, Brooks A, Kavaliunaite E, Kapatai G, et al. Whole-genome sequencing and epidemiological analysis do not provide evidence for cross-transmission of mycobacterium abscessus in a cohort of pediatric cystic fibrosis patients. Clin Infect Dis. 2015;60(7):1007–16.
178. Prevots DR, Adjemian J, Fernandez AG, Knowles MR, Olivier KN. Environmental risks for nontuberculous mycobacteria. Individual exposures and climatic factors in the cystic fibrosis population. Ann Am Thorac Soc. 2014;11(7):1032–8.
179. Bryant JM, Grogono DM, Rodriguez-Rincon D, Everall I, Brown KP, Moreno P, et al. Emergence and spread of a human-transmissible multidrug-resistant nontuberculous mycobacterium. Science (New York). 2016;354(6313):751–7.
180. Esther CR, Henry MM, Molina PL, Leigh MW. Nontuberculous mycobacterial infection in young children with cystic fibrosis. Pediatr Pulmonol. 2005;40(1):39–44.
181. Esther CR, Esserman DA, Gilligan P, Kerr A, Noone PG. Chronic Mycobacterium abscessus infection and lung function decline in cystic fibrosis. J Cyst Fibros. 2010;9(2):117–23.
182. Park IK, Olivier KN. Nontuberculous mycobacteria in cystic fibrosis and non-cystic fibrosis bronchiectasis. Semin Respir Crit Care Med. 2015;36(2):217–24.
183. Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis: executive summary. Thorax. 2016;71(1):88–90.
184. Scott JP, Ji Y, Kannan M, Wylam ME. Inhaled granulocyte-macrophage colony-stimulating factor for Mycobacterium abscessus in cystic fibrosis. Eur Respir J. 2018;51(4):1702127.
185. Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax. 2016;71(Suppl 1):i1–22.
186. American Academy of Pediatrics. Nontuberculous mycobacteria. In: Kimberlin D, Brady M, Jackson MA, Long S, editors. Red book. Elk Grove Village: American Academy of Pediatrics; 2018. p. 854–61.
187. Brown-Elliott BA, Nash KA, Wallace RJ Jr. Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with nontuberculous mycobacteria. Clin Microbiol Rev. 2012;25(3):545–82.
188. Cowman SA, Loebinger MR. Diagnosis of nontuberculous mycobacteria lung disease. Semin Respir Crit Care Med. 2018;39(3):343–50.
189. Ichiyama S, Iinuma Y, Yamori S, Hasegawa Y, Shimokata K, Nakashima N. Mycobacterium growth indicator tube testing in conjunction with the AccuProbe or the AMPLICOR-PCR assay for detecting and identifying mycobacteria from sputum samples. J Clin Microbiol. 1997;35(8):2022–5.
190. Blakemore R, Story E, Helb D, Kop J, Banada P, Owens MR, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. J Clin Microbiol. 2010;48(7):2495–501.
191. Lee H, Park HJ, Cho SN, Bai GH, Kim SJ. Species identification of mycobacteria by PCR-restriction fragment length polymorphism of the rpoB gene. J Clin Microbiol. 2000;38(8):2966–71.
192. Bannalikar AS, Verma R. Detection of Mycobacterium avium & M. tuberculosis from human sputum cultures by PCR-RFLP analysis of hsp65 gene & pncA PCR. Indian J Med Res. 2006;123(2):165–72.
193. Devallois A, Goh KS, Rastogi N. Rapid identification of mycobacteria to species level by PCR-restriction fragment length polymorphism analysis of the hsp65 gene and proposition of an algorithm to differentiate 34 mycobacterial species. J Clin Microbiol. 1997;35(11):2969–73.
194. Devallois A, Picardeau M, Paramasivan CN, Vincent V, Rastogi N. Molecular characterization of Mycobacterium avium complex isolates giving discordant results in AccuProbe tests by PCR-restriction enzyme analysis, 16S rRNA gene sequencing, and DT1-DT6 PCR. J Clin Microbiol. 1997;35(11):2767–72.
195. Dobner P, Feldmann K, Rifai M, Loscher T, Rinder H. Rapid identification of mycobacterial species by PCR amplification of hypervariable 16S rRNA gene promoter region. J Clin Microbiol. 1996;34(4):866–9.
196. Patel JB, Leonard DG, Pan X, Musser JM, Berman RE, Nachamkin I. Sequence-based identification of Mycobacterium species using the MicroSeq 500 16S rDNA bacterial identification system. J Clin Microbiol. 2000;38(1):246–51.
197. Roth A, Reischl U, Streubel A, Naumann L, Kroppenstedt RM, Habicht M, et al. Novel diagnostic algorithm for identification of mycobacteria using genus-specific amplification of the 16S-23S

rRNA gene spacer and restriction endonucleases. J Clin Microbiol. 2000;38(3):1094–104.
198. Suffys PN, da Silva Rocha A, de Oliveira M, Campos CE, Barreto AM, Portaels F, et al. Rapid identification of Mycobacteria to the species level using INNO-LiPA Mycobacteria, a reverse hybridization assay. J Clin Microbiol. 2001;39(12):4477–82.
199. Aravindhan V, Sulochana S, Narayanan S, Paramasivam CN, Narayanan PR. Identification & differentiation of Mycobacterium avium & M. intracellulare by PCR- RFLP assay using the groES gene. Indian J Med Res. 2007;126(6):575–9.
200. Alcaide F, Amlerova J, Bou G, Ceyssens PJ, Coll P, Corcoran D, et al. How to: identify non-tuberculous Mycobacterium species using MALDI-TOF mass spectrometry. Clin Microbiol Infect. 2018;24(6):599–603.
201. Ceyssens PJ, Soetaert K, Timke M, Van den Bossche A, Sparbier K, De Cremer K, et al. Matrix-assisted laser desorption ionization-time of flight mass spectrometry for combined species identification and drug sensitivity testing in mycobacteria. J Clin Microbiol. 2017;55(2):624–34.
202. Kodana M, Tarumoto N, Kawamura T, Saito T, Ohno H, Maesaki S, et al. Utility of the MALDI-TOF MS method to identify nontuberculous mycobacteria. J Infect Chemother. 2016;22(1):32–5.
203. Buckwalter SP, Olson SL, Connelly BJ, Lucas BC, Rodning AA, Walchak RC, et al. Evaluation of matrix-assisted laser desorption ionization-time of flight mass spectrometry for identification of mycobacterium species, Nocardia species, and other aerobic Actinomycetes. J Clin Microbiol. 2016;54(2):376–84.
204. Tudo G, Monte MR, Vergara A, Lopez A, Hurtado JC, Ferrer-Navarro M, et al. Implementation of MALDI-TOF MS technology for the identification of clinical isolates of Mycobacterium spp. in mycobacterial diagnosis. Eur J Clin Microbiol Infect Dis. 2015;34(8):1527–32.
205. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. WHO Guidelines Approved by the Guidelines Review Committee. Geneva; 2013.
206. Yin QQ, Jiao WW, Han R, Jiao AX, Sun L, Tian JL, et al. Rapid diagnosis of childhood pulmonary tuberculosis by Xpert MTB/RIF assay using bronchoalveolar lavage fluid. Biomed Res Int. 2014;2014:310194.
207. Mathew P, Kuo YH, Vazirani B, Eng RH, Weinstein MP. Are three sputum acid-fast bacillus smears necessary for discontinuing tuberculosis isolation? J Clin Microbiol. 2002;40(9):3482–4.
208. Nolan VG, Arnold SR, Bramley AM, Ampofo K, Williams DJ, Grijalva CG, et al. Etiology and impact of coinfections in children hospitalized with community-acquired pneumonia. J Infect Dis. 2018;218(2):179–88.
209. Costa C, Elia M, Astegiano S, Sidoti F, Terlizzi ME, Solidoro P, et al. Quantitative detection of Epstein-Barr virus in bronchoalveolar lavage from transplant and nontransplant patients. Transplantation. 2008;86(10):1389–94.
210. Costa C, Delsedime L, Solidoro P, Curtoni A, Bergallo M, Libertucci D, et al. Herpesviruses detection by quantitative real-time polymerase chain reaction in bronchoalveolar lavage and transbronchial biopsy in lung transplant: viral infections and histopathological correlation. Transplant Proc. 2010;42(4):1270–4.
211. Dioverti MV, Razonable RR. Cytomegalovirus. Microbiol Spectr. 2016;4(4) https://doi.org/10.1128/microbiolspec.DMIH2-0022-2015.
212. Liu P, Xu M, He L, Su L, Wang A, Fu P, et al. Epidemiology of respiratory pathogens in children with lower respiratory tract infections in Shanghai, China, from 2013 to 2015. Jpn J Infect Dis. 2018;71(1):39–44.
213. Esther CR Jr, Lin FC, Kerr A, Miller MB, Gilligan PH. Respiratory viruses are associated with common respiratory pathogens in cystic fibrosis. Pediatr Pulmonol. 2014;49(9):926–31.
214. Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics. 2004;113(4):701–7.
215. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet. 2011;377(9773):1264–75.
216. Reeves RM, Hardelid P, Gilbert R, Warburton F, Ellis J, Pebody RG. Estimating the burden of respiratory syncytial virus (RSV) on respiratory hospital admissions in children less than five years of age in England, 2007-2012. Influenza Other Respi Viruses. 2017;11(2):122–9.
217. Ogimi C, Waghmare AA, Kuypers JM, Xie H, Yeung CC, Leisenring WM, et al. Clinical significance of human coronavirus in bronchoalveolar lavage samples from hematopoietic cell transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2017;64(11):1532–9.
218. Chatzis O, Darbre S, Pasquier J, Meylan P, Manuel O, Aubert JD, et al. Burden of severe RSV disease among immunocompromised children and adults: a 10 year retrospective study. BMC Infect Dis. 2018;18(1):111.
219. Scheltema NM, Gentile A, Lucion F, Nokes DJ, Munywoki PK, Madhi SA, et al. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. Lancet Glob Health. 2017;5(10):e984–e91.
220. Azadeh N, Sakata KK, Saeed A, Mullon JJ, Grys TE, Limper AH, et al. Comparison of respiratory pathogen detection in upper versus lower respiratory tract samples using the BioFire FilmArray respiratory

panel in the immunocompromised host. Can Respir J. 2018;2018:2685723.
221. Lachant DJ, Croft DP, McGrane Minton H, Prasad P, Kottmann RM. Nasopharyngeal viral PCR in immunosuppressed patients and its association with virus detection in bronchoalveolar lavage by PCR. Respirology. 2017;22(6):1205–11.
222. Wurzel DF, Marchant JM, Clark JE, Mackay IM, Wang CY, Sloots TP, et al. Respiratory virus detection in nasopharyngeal aspirate versus bronchoalveolar lavage is dependent on virus type in children with chronic respiratory symptoms. J Clin Virol. 2013;58(4):683–8.
223. Restrepo-Gualteros SM, Jaramillo-Barberi LE, Gonzalez-Santos M, Rodriguez-Martinez CE, Perez GF, Gutierrez MJ, et al. Characterization of cytomegalovirus lung infection in non-HIV infected children. Viruses. 2014;6(5):2038–51.
224. Goussard P, Kling S, Gie RP, Nel ED, Heyns L, Rossouw GJ, et al. CMV pneumonia in HIV-infected ventilated infants. Pediatr Pulmonol. 2010;45(7):650–5.
225. Zampoli M, Morrow B, Hsiao NY, Whitelaw A, Zar HJ. Prevalence and outcome of cytomegalovirus-associated pneumonia in relation to human immunodeficiency virus infection. Pediatr Infect Dis J. 2011;30(5):413–7.
226. Gooskens J, Templeton KE, Claas EC, van Bussel MJ, Smit VT, Kroes AC. Quantitative detection of herpes simplex virus DNA in the lower respiratory tract. J Med Virol. 2007;79(5):597–604.
227. Wu JL, Ma HY, Lu CY, Chen JM, Lee PI, Jou ST, et al. Risk factors and outcomes of cytomegalovirus viremia in pediatric hematopoietic stem cell transplantation patients. J Microbiol Immunol Infect. 2017;50(3):307–13.
228. Rowe RG, Guo D, Lee M, Margossian S, London WB, Lehmann L. Cytomegalovirus infection in pediatric hematopoietic stem cell transplantation: risk factors for primary infection and cases of recurrent and late infection at a single center. Biol Blood Marrow Transplant. 2016;22(7):1275–83.
229. Chemaly RF, Yen-Lieberman B, Castilla EA, Reilly A, Arrigain S, Farver C, et al. Correlation between viral loads of cytomegalovirus in blood and bronchoalveolar lavage specimens from lung transplant recipients determined by histology and immunohistochemistry. J Clin Microbiol. 2004;42(5):2168–72.
230. Tan SK, Burgener EB, Waggoner JJ, Gajurel K, Gonzalez S, Chen SF, et al. Molecular and culture-based bronchoalveolar lavage fluid testing for the diagnosis of cytomegalovirus pneumonitis. Open Forum Infect Dis. 2016;3(1):ofv212.
231. Boeckh M, Stevens-Ayers T, Travi G, Huang ML, Cheng GS, Xie H, et al. Cytomegalovirus (CMV) DNA quantitation in bronchoalveolar lavage fluid from hematopoietic stem cell transplant recipients with CMV pneumonia. J Infect Dis. 2017;215(10):1514–22.
232. Lodding IP, Schultz HH, Jensen JU, Kirkby N, Perch M, Andersen C, et al. Cytomegalovirus viral load in bronchoalveolar lavage to diagnose lung transplant associated CMV pneumonia. Transplantation. 2018;102(2):326–32.
233. Chemaly RF, Yen-Lieberman B, Chapman J, Reilly A, Bekele BN, Gordon SM, et al. Clinical utility of cytomegalovirus viral load in bronchoalveolar lavage in lung transplant recipients. Am J Transplant. 2005;5(3):544–8.
234. Govender K, Jeena P, Parboosing R. Clinical utility of bronchoalveolar lavage cytomegalovirus viral loads in the diagnosis of cytomegalovirus pneumonitis in infants. J Med Virol. 2017;89(6):1080–7.
235. Beam E, Germer JJ, Lahr B, Yao JDC, Limper AH, Binnicker MJ, et al. Cytomegalovirus (CMV) DNA quantification in bronchoalveolar lavage fluid of immunocompromised patients with CMV pneumonia. Clin Transplant. 2018;32(1) https://doi.org/10.1111/ctr.13149.
236. Cunha BA, Eisenstein LE, Dillard T, Krol V. Herpes simplex virus (HSV) pneumonia in a heart transplant: diagnosis and therapy. Heart Lung. 2007;36(1):72–8.
237. Frangoul H, Wills M, Crossno C, Engel M, Domm J. Acyclovir-resistant herpes simplex virus pneumonia post-unrelated stem cell transplantation: a word of caution. Pediatr Transplant. 2007;11(8):942–4.
238. Gasparetto EL, Escuissato DL, Inoue C, Marchiori E, Müller NL. Herpes simplex virus type 2 pneumonia after bone marrow transplantation: high-resolution CT findings in 3 patients. J Thorac Imaging. 2005;20(2):71–3.
239. Linssen CF, Jacobs JA, Stelma FF, van Mook WN, Terporten P, Vink C, et al. Herpes simplex virus load in bronchoalveolar lavage fluid is related to poor outcome in critically ill patients. Intensive Care Med. 2008;34(12):2202–9.
240. Saugel B, Jakobus J, Huber W, Hoffmann D, Holzapfel K, Protzer U, et al. Herpes simplex virus in bronchoalveolar lavage fluid of medical intensive care unit patients: association with lung injury and outcome. J Crit Care. 2016;32:138–44.
241. Assink-de Jong E, Groeneveld AB, Pettersson AM, Koek A, Vandenbroucke-Grauls CM, Beishuizen A, et al. Clinical correlates of herpes simplex virus type 1 loads in the lower respiratory tract of critically ill patients. J Clin Virol. 2013;58(1):79–83.
242. Kotzbauer D, Frank G, Dong W, Shore S. Clinical and laboratory characteristics of disseminated herpes simplex virus infection in neonates. Hosp Pediatr. 2014;4(3):167–71.
243. Capretti MG, Marsico C, Lazzarotto T, Gabrielli L, Bagni A, De Angelis M, et al. Herpes Simplex Virus 1 infection: misleading findings in an infant with disseminated disease. New Microbiol. 2013;36(3):307–13.
244. Inokuchi R, Nakamura K, Sato H, Shinohara K, Aoki Y, Doi K, et al. Bronchial ulceration as a prognostic indicator for varicella pneumonia: case

report and systematic literature review. J Clin Virol. 2013;56(4):360–4.
245. Chiner E, Ballester I, Betlloch I, Blanquer J, Aguar MC, Blanquer R, et al. Varicella-zoster virus pneumonia in an adult population: has mortality decreased? Scand J Infect Dis. 2010;42(3):215–21.
246. Richaud C, Ngo MT, Agbessi CA, Boru B, Elkharrat D, Chinet T. Bronchial involvement in an immunocompetent adult with varicella pneumonia. Rev Mal Respir. 2008;25(1):59–62.
247. Libert N, Bigaillon C, Chargari C, Bensalah M, Muller V, Merat S, et al. Epstein-Barr virus reactivation in critically ill immunocompetent patients. Biomed J. 2015;38(1):70–6.
248. Banks CA, Meier JD, Stallworth CR, White DR. Recurrent posttransplant lymphoproliferative disorder involving the larynx and trachea: case report and review of the literature. Ann Otol Rhinol Laryngol. 2012;121(5):291–5.
249. O'Neill AF, Adil EA, Irace AL, Neff L, Davis IJ, Perez-Atayde AR, et al. Post-transplant lymphoproliferative disorder of the pediatric airway: Presentation and management. Int J Pediatr Otorhinolaryngol. 2016;86:218–23.
250. Feuillet S, Meignin V, Briere J, Brice P, Rocha V, Socie G, et al. Endobronchial Epstein-Barr Virus associated post-transplant lymphoproliferative disorder in hematopoietic stem cell transplantation. Clin Med Case Rep. 2009;2:11–5.
251. Fortes HR, von Ranke FM, Escuissato DL, Araujo Neto CA, Zanetti G, Hochhegger B, et al. Recurrent respiratory papillomatosis: a state-of-the-art review. Respir Med. 2017;126:116–21.
252. Pritt BS, Aubry MC. Histopathology of viral infections of the lung. Semin Diagn Pathol. 2017;34(6):510–7.
253. Smyth RL, Higenbottam TW, Scott JP, Wreghitt TG, Stewart S, Clelland CA, et al. Herpes simplex virus infection in heart-lung transplant recipients. Transplantation. 1990;49(4):735–9.
254. Costa C, Libertucci D, Solidoro P, Sinesi F, Bergallo M, Margio S, et al. Rapid shell vial culture for the detection of respiratory viruses from bronchoalveolar lavage in immunocompromised patients. Panminerva Med. 2007;49(1):1–6.
255. Marcos MA, Esperatti M, Torres A. Viral pneumonia. Curr Opin Infect Dis. 2009;22(2):143–7.
256. Prendergast C, Papenburg J. Rapid antigen-based testing for respiratory syncytial virus: moving diagnostics from bench to bedside? Future Microbiol. 2013;8(4):435–44.
257. Chartrand C, Tremblay N, Renaud C, Papenburg J. Diagnostic accuracy of rapid antigen detection tests for respiratory syncytial virus infection: systematic review and meta-analysis. J Clin Microbiol. 2015;53(12):3738–49.
258. Chartrand C, Leeflang MM, Minion J, Brewer T, Pai M. Accuracy of rapid influenza diagnostic tests: a meta-analysis. Ann Intern Med. 2012;156(7):500–11.
259. Bennett JE. Introduction to Mycoses. In: Bennett J, Dolin R, Blaser M, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia, PA: Elsevier; 2016.
260. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813–21.
261. Anantasit N, Nuntacharruksa N, Incharoen P, Preutthipan A. Clinical and pathological correlation in pediatric invasive pulmonary Aspergillosis. Front Pediatr. 2018;6:31.
262. Maturu VN, Agarwal R. Prevalence of Aspergillus sensitization and allergic bronchopulmonary aspergillosis in cystic fibrosis: systematic review and meta-analysis. Clin Exp Allergy. 2015;45(12):1765–78.
263. Agarwal R, Aggarwal AN, Gupta D, Jindal SK. Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis in patients with bronchial asthma: systematic review and meta-analysis. Int J Tuberc Lung Dis. 2009;13(8):936–44.
264. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy. 2013;43(8):850–73.
265. Neofytos D, Fishman JA, Horn D, Anaissie E, Chang CH, Olyaei A, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis. 2010;12(3):220–9.
266. Neofytos D, Horn D, Anaissie E, Steinbach W, Olyaei A, Fishman J, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis. 2009;48(3):265–73.
267. Krenke R, Grabczak EM. Tracheobronchial manifestations of Aspergillus infections. Scientific World Journal. 2011;11:2310–29.
268. Moura S, Cerqueira L, Almeida A. Invasive pulmonary aspergillosis: current diagnostic methodologies and a new molecular approach. Eur J Clin Microbiol Infect Dis. 2018;37(8):1393–403.
269. Walzer P, Smulian A, Miller R. Pneumocystis species. In: Bennett J, Dolin R, Blaser M, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia, PA: Elsevier; 2016.
270. Inagaki K, Blackshear C, Hobbs CV. Pneumocystis infection in children: national trends and characteristics in the United States, 1997-2012. Pediatr Infect Dis J. 2019;38(3):241–7.
271. Vera C, Aguilar YA, Velez LA, Rueda ZV. High transient colonization by Pneumocystis jirovecii between mothers and newborn. Eur J Pediatr. 2017;176(12):1619–27.

272. Oladele RO, Otu AA, Richardson MD, Denning DW. Diagnosis and management of Pneumocystis pneumonia in resource-poor settings. J Health Care Poor Underserved. 2018;29(1):107–58.
273. Toma P, Bertaina A, Castagnola E, Colafati GS, D'Andrea ML, Finocchi A, et al. Fungal infections of the lung in children. Pediatr Radiol. 2016;46(13):1856–65.
274. Fillaux J, Malvy S, Alvarez M, Fabre R, Cassaing S, Marchou B, et al. Accuracy of a routine real-time PCR assay for the diagnosis of Pneumocystis jirovecii pneumonia. J Microbiol Methods. 2008;75(2):258–61.
275. Lease ED, Alexander BD. Fungal diagnostics in pneumonia. Semin Respir Crit Care Med. 2011;32(6):663–72.
276. Summah H, Zhu YG, Falagas ME, Vouloumanou EK, Qu JM. Use of real-time polymerase chain reaction for the diagnosis of Pneumocystis pneumonia in immunocompromised patients: a meta-analysis. Chin Med J (Engl). 2013;126(10):1965–73.
277. Fan LC, Lu HW, Cheng KB, Li HP, Xu JF. Evaluation of PCR in bronchoalveolar lavage fluid for diagnosis of Pneumocystis jirovecii pneumonia: a bivariate meta-analysis and systematic review. PLoS One. 2013;8(9):e73099.
278. Karageorgopoulos DE, Qu JM, Korbila IP, Zhu YG, Vasileiou VA, Falagas ME. Accuracy of beta-D-glucan for the diagnosis of Pneumocystis jirovecii pneumonia: a meta-analysis. Clin Microbiol Infect. 2013;19(1):39–49.
279. Katragkou A, Fisher BT, Groll AH, Roilides E, Walsh TJ. Diagnostic imaging and invasive fungal diseases in children. J Pediatric Infect Dis Soc. 2017;6(suppl_1):S22–31.
280. Durairaj L, Mohamad Z, Launspach JL, Ashare A, Choi JY, Rajagopal S, et al. Patterns and density of early tracheal colonization in intensive care unit patients. J Crit Care. 2009;24(1):114–21.
281. Meersseman W, Lagrou K, Spriet I, Maertens J, Verbeken E, Peetermans WE, et al. Significance of the isolation of Candida species from airway samples in critically ill patients: a prospective, autopsy study. Intensive Care Med. 2009;35(9):1526–31.
282. Terraneo S, Ferrer M, Martin-Loeches I, Esperatti M, Di Pasquale M, Giunta V, et al. Impact of Candida spp. isolation in the respiratory tract in patients with intensive care unit-acquired pneumonia. Clin Microbiol Infect. 2016;22(1):94.e1–8.
283. AbdulWahab A, Salah H, Chandra P, Taj-Aldeen SJ. Persistence of Candida dubliniensis and lung function in patients with cystic fibrosis. BMC Res Notes. 2017;10(1):326.
284. Shirley RM, Baddley JW. Cryptococcal lung disease. Curr Opin Pulm Med. 2009;15(3):254–60.
285. Fyfe M, MacDougall L, Romney M, Starr M, Pearce M, Mak S, et al. Cryptococcus gattii infections on Vancouver Island, British Columbia, Canada: emergence of a tropical fungus in a temperate environment. Can Commun Dis Rep. 2008;34(6):1–12.
286. Shaheen AA, Somayaji R, Myers R, Mody CH. Epidemiology and trends of cryptococcosis in the United States from 2000 to 2007: A population-based study. Int J STD AIDS. 2018;29(5):453–60.
287. Liu L, Guo L, Liu Y, Chen T, Li S, Yang Y, et al. Clinical characteristics and prognosis of pediatric cryptococcosis in Beijing Children's Hospital, 2002-2014. Eur J Pediatr. 2017;176(9):1235–44.
288. Lamoth F, Alexander BD. Nonmolecular methods for the diagnosis of respiratory fungal infections. Clin Lab Med. 2014;34(2):315–36.
289. Lass-Florl C. Current challenges in the diagnosis of fungal infections. Methods Mol Biol (Clifton, NJ). 2017;1508:3–15.
290. Pappas PG, Perfect JR, Cloud GA, Larsen RA, Pankey GA, Lancaster DJ, et al. Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. Clin Infect Dis. 2001;33(5):690–9.
291. Xie X, Xu B, Yu C, Chen M, Yao D, Xu X, et al. Clinical analysis of pulmonary cryptococcosis in non-HIV patients in south China. Int J Clin Exp Med. 2015;8(3):3114–9.
292. Kralovic SM, Rhodes JC. Utility of routine testing of bronchoalveolar lavage fluid for cryptococcal antigen. J Clin Microbiol. 1998;36(10):3088–9.
293. Baughman RP, Rhodes JC, Dohn MN, Henderson H, Frame PT. Detection of cryptococcal antigen in bronchoalveolar lavage fluid: a prospective study of diagnostic utility. Am Rev Respir Dis. 1992;145(5):1226–9.
294. Senghor Y, Guitard J, Angoulvant A, Hennequin C. Cryptococcal antigen detection in bronchoalveolar lavage fluid. Med Mycol. 2018;56(6):774–7.
295. Kontoyiannis DP, Lewis RE. Agents of mucormycosis and entomophthoramycosis. In: Bennett J, Dolin R, Blaser M, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia, PA: Elsevier; 2015.
296. Walsh TJ, Gamaletsou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis. 2012;54(Suppl 1):S55–60.
297. McBride JA, Gauthier GM, Klein BS. Clinical manifestations and treatment of blastomycosis. Clin Chest Med. 2017;38(3):435–49.
298. Goughenour KD, Rappleye CA. Antifungal therapeutics for dimorphic fungal pathogens. Virulence. 2017;8(2):211–21.
299. Baddley JW, Winthrop KL, Patkar NM, Delzell E, Beukelman T, Xie F, et al. Geographic distribution of endemic fungal infections among older persons, United States. Emerg Infect Dis. 2011;17(9):1664–9.
300. Martinez R. New trends in paracoccidioidomycosis epidemiology. J Fungi (Basel). 2017;3(1):1.
301. Hage CA, Knox KS, Wheat LJ. Endemic mycoses: overlooked causes of community acquired pneumonia. Respir Med. 2012;106(6):769–76.

302. McKinsey DS, McKinsey JP. Pulmonary histoplasmosis. Semin Respir Crit Care Med. 2011;32(6):735–44.
303. Denning DW, Chakrabarti A. Pulmonary and sinus fungal diseases in non-immunocompromised patients. Lancet Infect Dis. 2017;17(11):e357–e66.
304. Wheat LJ. Approach to the diagnosis of the endemic mycoses. Clin Chest Med. 2009;30(2):379–89. viii.
305. Hage CA, Azar MM, Bahr N, Loyd J, Wheat LJ. Histoplasmosis: up-to-date evidence-based approach to diagnosis and management. Semin Respir Crit Care Med. 2015;36(5):729–45.
306. Hage CA, Wheat LJ. Diagnosis of pulmonary histoplasmosis using antigen detection in the bronchoalveolar lavage. Expert Rev Respir Med. 2010;4(4):427–9.
307. Hage CA, Ribes JA, Wengenack NL, Baddour LM, Assi M, McKinsey DS, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis. 2011;53(5):448–54.
308. Tarrand JJ, Lichterfeld M, Warraich I, Luna M, Han XY, May GS, et al. Diagnosis of invasive septate mold infections. A correlation of microbiological culture and histologic or cytologic examination. Am J Clin Pathol. 2003;119(6):854–8.
309. Lehrnbecher T, Robinson PD, Fisher BT, Castagnola E, Groll AH, Steinbach WJ, et al. Galactomannan, beta-D-glucan, and polymerase chain reaction-based assays for the diagnosis of invasive fungal disease in pediatric cancer and hematopoietic stem cell transplantation: a systematic review and meta-analysis. Clin Infect Dis. 2016;63(10):1340–8.
310. Loeffler J, Hafner J, Mengoli C, Wirth C, Heussel CP, Loffler C, et al. Prospective biomarker screening for diagnosis of invasive aspergillosis in high-risk pediatric patients. J Clin Microbiol. 2017;55(1):101–9.
311. Avni T, Levy I, Sprecher H, Yahav D, Leibovici L, Paul M. Diagnostic accuracy of PCR alone compared to galactomannan in bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis: a systematic review. J Clin Microbiol. 2012;50(11):3652–8.
312. Trubiano JA, Dennison AM, Morrissey CO, Chua KY, Halliday CL, Chen SC, et al. Clinical utility of panfungal polymerase chain reaction for the diagnosis of invasive fungal disease: a single center experience. Med Mycol. 2016;54(2):138–46.
313. Hage CA, Davis TE, Fuller D, Egan L, Witt JR 3rd, Wheat LJ, et al. Diagnosis of histoplasmosis by antigen detection in BAL fluid. Chest. 2010;137(3):623–8.
314. Huang YT, Hung CC, Liao CH, Sun HY, Chang SC, Chen YC. Detection of circulating galactomannan in serum samples for diagnosis of Penicillium marneffei infection and cryptococcosis among patients infected with human immunodeficiency virus. J Clin Microbiol. 2007;45(9):2858–62.
315. Park SY, Lee SO, Choi SH, Sung H, Kim MN, Choi CM, et al. Aspergillus galactomannan antigen assay in bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis. J Infect. 2010;61(6):492–8.
316. de Mol M, de Jongste JC, van Westreenen M, Merkus PJ, de Vries AH, Hop WC, et al. Diagnosis of invasive pulmonary aspergillosis in children with bronchoalveolar lavage galactomannan. Pediatr Pulmonol. 2013;48(8):789–96.
317. Desai R, Ross LA, Hoffman JA. The role of bronchoalveolar lavage galactomannan in the diagnosis of pediatric invasive aspergillosis. Pediatr Infect Dis J. 2009;28(4):283–6.
318. Zhang S, Wang S, Wan Z, Li R, Yu J. The diagnosis of invasive and noninvasive pulmonary aspergillosis by serum and bronchoalveolar lavage fluid galactomannan assay. Biomed Res Int. 2015;2015:943691.
319. Zhou W, Li H, Zhang Y, Huang M, He Q, Li P, et al. Diagnostic value of galactomannan antigen test in serum and bronchoalveolar lavage fluid samples from patients with nonneutropenic invasive pulmonary aspergillosis. J Clin Microbiol. 2017;55(7):2153–61.
320. Nguyen MH, Leather H, Clancy CJ, Cline C, Jantz MA, Kulkarni V, et al. Galactomannan testing in bronchoalveolar lavage fluid facilitates the diagnosis of invasive pulmonary aspergillosis in patients with hematologic malignancies and stem cell transplant recipients. Biol Blood Marrow Transplant. 2011;17(7):1043–50.
321. Zhang XB, Chen GP, Lin QC, Lin X, Zhang HY, Wang JH. Bronchoalveolar lavage fluid galactomannan detection for diagnosis of invasive pulmonary aspergillosis in chronic obstructive pulmonary disease. Med Mycol. 2013;51(7):688–95.
322. Pasqualotto AC, Xavier MO, Sanchez LB, de Oliveira Costa CD, Schio SM, Camargo SM, et al. Diagnosis of invasive aspergillosis in lung transplant recipients by detection of galactomannan in the bronchoalveolar lavage fluid. Transplantation. 2010;90(3):306–11.
323. Mohammadi S, Khalilzadeh S, Goudarzipour K, Hassanzad M, Mahdaviani A, Aarabi N, et al. Bronchoalveolar galactomannan in invasive pulmonary aspergillosis: a prospective study in pediatric patients. Med Mycol. 2015;53(7):709–16.
324. He S, Hang JP, Zhang L, Wang F, Zhang DC, Gong FH. A systematic review and meta-analysis of diagnostic accuracy of serum 1,3-beta-D-glucan for invasive fungal infection: focus on cutoff levels. J Microbiol Immunol Infect. 2015;48(4):351–61.
325. Egger M, Pruller F, Raggam R, Divjak MK, Kurath-Koller S, Lackner H, et al. False positive serum levels of (1-3)-ss-D-Glucan after infusion of intravenous immunoglobulins and time to normalisation. J Infect. 2018;76(2):206–10.
326. Liss B, Cornely OA, Hoffmann D, Dimitriou V, Wisplinghoff H. 1,3-ss-D-glucan concentrations in blood products predict false positive post-transfusion results. Mycoses. 2016;59(1):39–42.
327. Goudjil S, Chazal C, Moreau F, Leke A, Kongolo G, Chouaki T. Blood product transfusions are associated with an increase in serum (1-3)-beta-d-glucan in

infants during the initial hospitalization in neonatal intensive care unit (NICU). J Matern Fetal Neonatal Med. 2017;30(8):933–7.
328. Calitri C, Caviglia I, Cangemi G, Furfaro E, Bandettini R, Fioredda F, et al. Performance of 1,3-beta-D-glucan for diagnosing invasive fungal diseases in children. Mycoses. 2017;60(12):789–95.
329. Shabaan AE, Elbaz LM, El-Emshaty WM, Shouman B. Role of serum 1,3beta-d-glucan assay in early diagnosis of invasive fungal infections in a neonatal intensive care unit. J Pediatr (Rio J). 2018;94(5):559–65.
330. Shi XY, Liu Y, Gu XM, Hao SY, Wang YH, Yan D, et al. Diagnostic value of (1 --> 3)-beta-D-glucan in bronchoalveolar lavage fluid for invasive fungal disease: a meta-analysis. Respir Med. 2016;117:48–53.
331. Salerno D, Mushatt D, Myers L, Zhuang Y, de la Rua N, Calderon EJ, et al. Serum and bal beta-D-glucan for the diagnosis of Pneumocystis pneumonia in HIV positive patients. Respir Med. 2014;108(11):1688–95.
332. Maguire JH. Introduction to helminth infections. In: Bennett J, Dolin R, Blaser M, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia, PA: Elsevier; 2015.
333. Korpe PS, Ravdin JI, Petri WA. Introduction to protozoal diseases. In: Bennett J, Dolin R, Blaser M, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia, PA: Elsevier; 2015.
334. Taylor WRJ, Hanson J, Turner GDH, White NJ, Dondorp AM. Respiratory manifestations of malaria. Chest. 2012;142(2):492–505.
335. de Souza GK, Costa AN, Apanavicius A, Teixeira FB, Fernandes CJ, Helito AS, et al. Tomographic findings of acute pulmonary toxoplasmosis in immunocompetent patients. BMC Pulm Med. 2014;14:185.
336. Rey MF, Mary C, Sanguinetti D, Ranque S, Bartoli C, L'Ollivier C. Successful treatment of pulmonary and cerebral toxoplasmosis associated with pneumocystis pneumonia in an HIV patient. Diseases (Basel). 2017;5(4):35.
337. Sumi M, Norose K, Hikosaka K, Kaiume H, Takeda W, Kirihara T, et al. Clinical characteristics and computed tomography findings of pulmonary toxoplasmosis after hematopoietic stem cell transplantation. Int J Hematol. 2016;104(6):729–40.
338. Roth A, Roth B, Hoffken G, Steuber S, Khalifa KI, Janitschke K. Application of the polymerase chain reaction in the diagnosis of pulmonary toxoplasmosis in immunocompromised patients. Eur J Clin Microbiol Infect Dis. 1992;11(12):1177–81.
339. Diehl AR, Dos Santos RP, Zimmerman R, Luz PL, Weiss T, Jacobson P, et al. Microscopy and polymerase chain reaction detection of Leishmania chagasi in the pleural and ascitic fluid of a patient with AIDS: case report and review of diagnosis and therapy of visceral leishmaniasis. Can J Infect Dis Med Microbiol. 2004;15(4):231–4.
340. Zakaria A, Al-Share B, Al Asad K. Primary pulmonary amebiasis complicated with multicystic empyema. Case Rep Pulmonol. 2016;2016:8709347.
341. Shamsuzzaman SM, Hashiguchi Y. Thoracic amebiasis. Clin Chest Med. 2002;23(2):479–92.
342. Cunha BA, Nausheen S, Szalda D. Pulmonary complications of babesiosis: case report and literature review. Euro J Clin Microbiol Infect Dis. 2007;26(7):505–8.
343. Cheepsattayakorn A, Cheepsattayakorn R. Parasitic pneumonia and lung involvement. Biomed Res Int. 2014;2014:874021.
344. Vasilakopoulou A, Dimarongona K, Samakovli A, Papadimitris K, Avlami A. Balantidium coli pneumonia in an immunocompromised patient. Scand J Infect Dis. 2003;35(2):144–6.
345. Anargyrou K, Petrikkos GL, Suller MT, Skiada A, Siakantaris MP, Osuntoyinbo RT, et al. Pulmonary Balantidium coli infection in a leukemic patient. Am J Hematol. 2003;73(3):180–3.
346. Reina FT, Ribeiro CA, Araujo RS, Matte MH, Castanho RE, Tanaka II, et al. Intestinal and pulmonary infection by Cryptosporidium parvum in two patients with HIV/AIDS. Rev Inst Med Trop Sao Paulo. 2016;58:21.
347. Poirot JL, Deluol AM, Antoine M, Heyer F, Cadranel J, Meynard JL, et al. Broncho-pulmonary cryptosporidiosis in four HIV-infected patients. J Eukaryot Microbiol. 1996;43(5):78s–9s.
348. Lanzafame M, Bonora S, Di Perri G, Allegranzi B, Guasparri I, Cazzadori A, et al. Microsporidium species in pulmonary cavitary lesions of AIDS patients infected with Rhodococcus equi. Clin Infect Dis. 1997;25(4):926–7.
349. Yao G, Zhou B, Zeng L. Imaging characteristics of bronchopulmonary Lophomonas blattarum infection: case report and literature review. J Thorac Imaging. 2009;24(1):49–51.
350. Saldana NG, Mendoza FJO, Larrauri FR, Trujillo DMG, Montoya EV, De La Garza EA, et al. Bronchopulmonary infection by Lophomonas blattarum in a pediatric patient after hematopoietic progenitor cell transplantation: first report in Mexico. J Thorac Dis. 2017;9(10):E899–e902.
351. Zhang X, Xu L, Wang LL, Liu S, Li J, Wang X. Bronchopulmonary infection with Lophomonas blattarum: a case report and literature review. J Int Med Res. 2011;39(3):944–9.
352. Barratt JL, Harkness J, Marriott D, Ellis JT, Stark D. Importance of nonenteric protozoan infections in immunocompromised people. Clin Microbiol Rev. 2010;23(4):795–836.
353. Schwartz C, Hams E, Fallon PG. Helminth modulation of lung inflammation. Trends Parasitol. 2018;34(5):388–403.
354. Craig JM, Scott AL. Helminths in the lungs. Parasite Immunol. 2014;36(9):463–74.

355. Loukas A, Hotez PJ, Diemert D, Yazdanbakhsh M, McCarthy JS, Correa-Oliveira R, et al. Hookworm infection. Nat Rev Dis Primers. 2016;2:16088.
356. Allen J, Wert M. Eosinophilic Pneumonias. J Allergy Clin Immunol Pract. 2018;6(5):1455–61.
357. Pavlin BI, Kozarsky P, Cetron MS. Acute pulmonary schistosomiasis in travelers: case report and review of the literature. Travel Med Infect Dis. 2012;10(5–6):209–19.
358. Schwartz E. Pulmonary schistosomiasis. Clin Chest Med. 2002;23(2):433–43.
359. Dantas-Torres F, Otranto D. Dirofilariosis in the Americas: a more virulent Dirofilaria immitis? Parasit Vectors. 2013;6(1):288.
360. Li CY, Chang YL, Lee YC. Human pulmonary dirofilariasis coexisting with intercostal neurilemmoma: a case report and literature review. J Formos Med Assoc. 2013;112(10):644–7.
361. Park KH, Kim YS, Kim SK, Choi NC, Kwon OY, Lim B, et al. Toxocara canis-associated myelitis with eosinophilic pneumonia. Exp Neurobiol. 2016;25(3):139–42.
362. Mazur-Melewska K, Jonczyk-Potoczna K, Kemnitz P, Mania A, Figlerowicz M, Sluzewski W. Pulmonary presentation of Toxocara sp. infection in children. Pneumonol Alergol Pol. 2015;83(4):250–5.
363. Blair D. Paragonimiasis. Adv Exp Med Biol. 2014;766:115–52.
364. Lamberton PH, Jourdan PM. Human ascariasis: diagnostics update. Curr Trop Med Rep. 2015;2(4):189–200.
365. Gupta N, Ray A, Ghosh S, Malla S, Vyas S. First things first: Importance of eosinophil count in diagnosing occult parasites. Drug Discov Ther. 2018;12(1):55–7.
366. Kilic D, Tercan F, Sahin E, Bilen A, Hatipoglu A. Unusual radiologic manifestations of the echinococcus infection in the thorax. J Thorac Imaging. 2006;21(1):32–6.
367. Vaideeswar P, Agnihotri MA, Hira P. Unusual manifestations of pleuro-pulmonary hydatidosis. Indian J Pathol Microbiol. 2012;55(1):111–2.
368. Sarkar M, Pathania R, Jhobta A, Thakur BR, Chopra R. Cystic pulmonary hydatidosis. Lung India. 2016;33(2):179–91.
369. Ali SR, Mehta AC. Alive in the airways: live endobronchial foreign bodies. Chest. 2017;151(2):481–91.
370. Gan RW, Gohil R, Belfield K, Davies P, Daniel M. Acute airway obstruction by Ascaris lumbricoides in a 14-month-old boy. Int J Pediatr Otorhinolaryngol. 2014;78(10):1795–8.
371. Bailey JK, Warner P. Respiratory arrest from Ascaris lumbricoides. Pediatrics. 2010;126(3):e712–5.
372. Nabeya D, Haranaga S, Parrott GL, Kinjo T, Nahar S, Tanaka T, et al. Pulmonary strongyloidiasis: assessment between manifestation and radiological findings in 16 severe strongyloidiasis cases. BMC Infect Dis. 2017;17(1):320.
373. Alsharif A, Sodhi A, Murillo LC, Headley AS, Kadaria D. Wait!!! no steroids for this asthma. Am J Case Rep. 2015;16:398–400.
374. Rajapurkar M, Hegde U, Rokhade M, Gang S, Gohel K. Respiratory hyperinfection with Strongyloides stercoralis in a patient with renal failure. Nat Clin Pract Nephrol. 2007;3(10):573–7.
375. Pozio E, Gomez Morales MA, Dupouy-Camet J. Clinical aspects, diagnosis and treatment of trichinellosis. Expert Rev Anti Infect Ther. 2003;1(3):471–82.
376. Genetu Bayih A, Debnath A, Mitre E, Huston CD, Laleu B, Leroy D, et al. Susceptibility testing of medically important parasites. Clin Microbiol Rev. 2017;30(3):647–69.
377. Buonfrate D, Requena-Mendez A, Angheben A, Cinquini M, Cruciani M, Fittipaldo A, et al. Accuracy of molecular biology techniques for the diagnosis of Strongyloides stercoralis infection-a systematic review and meta-analysis. PLoS Negl Trop Dis. 2018;12(2):e0006229.
378. Schijman AG. Molecular diagnosis of Trypanosoma cruzi. Acta Trop. 2018;184:59–66.
379. Amir A, Cheong FW, De Silva JR, Lau YL. Diagnostic tools in childhood malaria. Parasit Vectors. 2018;11(1):53.
380. Singh R, Singh DP, Gupta R, Savargaonkar D, Singh OP, Nanda N, et al. Comparison of three PCR-based assays for the non-invasive diagnosis of malaria: detection of Plasmodium parasites in blood and saliva. Euro J Clin Microbiol Infect Dis. 2014;33(9):1631–9.
381. Murat JB, Hidalgo HF, Brenier-Pinchart MP, Pelloux H. Human toxoplasmosis: which biological diagnostic tests are best suited to which clinical situations? Expert Rev Anti Infect Ther. 2013;11(9):943–56.
382. Adeyemo FE, Singh G, Reddy P, Stenstrom TA. Methods for the detection of Cryptosporidium and Giardia: from microscopy to nucleic acid based tools in clinical and environmental regimes. Acta Trop. 2018;184:15–28.
383. Garcia LS, Arrowood M, Kokoskin E, Paltridge GP, Pillai DR, Procop GW, et al. Laboratory diagnosis of parasites from the gastrointestinal tract. Clin Microbiol Rev. 2018;31(1):e00025–17.
384. Boland JM, Pritt BS. Histopathology of parasitic infections of the lung. Semin Diagn Pathol. 2017;34(6):550–9.
385. Zhu H, Min X, Li S, Feng M, Zhang G, Yi X. Amebic lung abscess with coexisting lung adenocarcinoma: a unusual case of amebiasis. Int J Clin Exp Pathol. 2014;7(11):8251–4.
386. Hizem A, M'rad S, Oudni-M'rad M, Mestiri S, Hammedi F, Mezhoud H, et al. Molecular genotyping of Echinococcus granulosus using formalin-fixed paraffin-embedded preparations from human isolates in unusual tissue sites. J Helminthol. 2016;90(4):417–21.
387. Rivasi F, Boldorini R, Criante P, Leutner M, Pampiglione S. Detection of Dirofilaria (Nochtiella) repens DNA by polymerase chain reaction in embedded paraffin tissues from two human pulmonary locations. APMIS. 2006;114(7–8):567–74.

388. Gobbi F, Formenti F, Perandin F, Buonfrate D, Angheben A, Paiano S, et al. Real-time polymerase chain reaction assay on bronchoalveolar lavage: an alternative method for diagnosing chronic pulmonary schistosomiasis? Am J Trop Med Hyg. 2017;97(6):1808–9.
389. Izadi M, Jonaidi Jafari N, Mahmoodzadeh Poornaki A, Sadraei J, Rezavand B, Mirzaei HR, et al. Detection of Toxoplasma gondii from clinical specimens of patients receiving renal transplant using ELISA and PCR. Nephrourol Mon. 2013;5(5):983–7.
390. Özkoç S, Bayram Delibaş S, Akısü Ç. Evaluation of pulmonary microsporidiosis in iatrogenically immunosuppressed patients. Tuberk Toraks. 2016;64(1):9–16.
391. Desoubeaux G, Cabanne E, Franck-Martel C, Gombert M, Gyan E, Lissandre S, et al. Pulmonary toxoplasmosis in immunocompromised patients with interstitial pneumonia: a single-centre prospective study assessing PCR-based diagnosis. J Clin Pathol. 2016;69(8):726–30.
392. Montresor A, Crompton DWT, Hall A, Bundy DAP, Savioli L. Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis at community level: a guide for managers of control programmes. Geneva: World Health Organization; 1998.
393. Itoh N, Tsukahara M, Yamasaki H, Morishima Y, Sugiyama H, Kurai H. Paragonimus westermani infection mimicking recurrent lung cancer: a case report. J Infect Chemother. 2016;22(12):815–8.
394. Guerrero-Wooley R, Aranda-Aguirre E, Li W, Wilkin A, Palavecino E. Case report: Strongyloides stercoralis hyperinfection in a patient with chronic lymphocytic leukemia. Am J Trop Med Hyg. 2017;97(5):1629–31.
395. Wang LF, Xu L, Luo SQ, Xie H, Chen W, Wu ZD, et al. Diagnosis of Strongyloides stercoralis by morphological characteristics combine with molecular biological methods. Parasitol Res. 2017;116(4):1159–63.
396. Kinjo T, Tsuhako K, Nakazato I, Ito E, Sato Y, Koyanagi Y, et al. Extensive intra-alveolar haemorrhage caused by disseminated strongyloidiasis. Int J Parasitol. 1998;28(2):323–30.
397. Tanyuksel M, Petri WA Jr. Laboratory diagnosis of amebiasis. Clin Microbiol Rev. 2003;16(4):713–29.
398. Chaudhry IU, Manah W, Alghamdi M, Mutairi H. A rare cause of asymptomatic solitary pulmonary nodule: adult Schistosoma worm. BMJ Case Rep. 2014;2014:bcr2013202840.
399. Yasar Z, Acat M, Turgut E, Onaran H, Dincer HE, Arda N, et al. Diagnosis of pulmonary hydatid cyst by bronchoscopy. J Bronchology Interv Pulmonol. 2015;22(4):343–6.
400. Komurcuoglu B, Ozkaya S, Cirak AK, Yalniz E, Polat G. Pulmonary hydatid cyst: the characteristics of patients and diagnostic efficacy of bronchoscopy. Exp Lung Res. 2012;38(6):277–80.
401. Prasad R, Goel MK, Mukerji PK, Agarwal PK. Microfilaria in bronchial aspirate. Indian J Chest Dis Allied Sci. 1994;36(4):223–5.
402. Anupindi L, Sahoo R, Rao RV, Verghese G, Rao PV. Microfilariae in bronchial brushing cytology of symptomatic pulmonary lesions. A report of two cases. Acta Cytol. 1993;37(3):397–9.
403. Cui L, Morris A, Huang L, Beck JM, Twigg HL 3rd, von Mutius E, et al. The microbiome and the lung. Ann Am Thorac Soc. 2014;11(Suppl 4):S227–32.
404. Pendleton KM, Erb-Downward JR, Bao Y, Branton WR, Falkowski NR, Newton DW, et al. Rapid pathogen identification in bacterial pneumonia using real-time metagenomics. Am J Respir Crit Care Med. 2017;196(12):1610–2.
405. Dickson RP, Erb-Downward JR, Prescott HC, Martinez FJ, Curtis JL, Lama VN, et al. Analysis of culture-dependent versus culture-independent techniques for identification of bacteria in clinically obtained bronchoalveolar lavage fluid. J Clin Microbiol. 2014;52(10):3605–13.
406. Marsh RL, Kaestli M, Chang AB, Binks MJ, Pope CE, Hoffman LR, et al. The microbiota in bronchoalveolar lavage from young children with chronic lung disease includes taxa present in both the oropharynx and nasopharynx. Microbiome. 2016;4(1):37.
407. Marsh RL, Smith-Vaughan HC, Chen ACH, Marchant JM, Yerkovich ST, Gibson PG, et al. Multiple respiratory microbiota profiles are associated with lower airway inflammation in children with protracted bacterial bronchitis. Chest. 2019;155(4):778–86.
408. Zemanick ET, Wagner BD, Robertson CE, Ahrens RC, Chmiel JF, Clancy JP, et al. Airway microbiota across age and disease spectrum in cystic fibrosis. Eur Respir J. 2017;50(5):1700832.
409. Harris JK, De Groote MA, Sagel SD, Zemanick ET, Kapsner R, Penvari C, et al. Molecular identification of bacteria in bronchoalveolar lavage fluid from children with cystic fibrosis. Proc Natl Acad Sci U S A. 2007;104(51):20529–33.
410. Prevaes SM, de Winter-de Groot KM, Janssens HM, de Steenhuijsen Piters WA, Tramper-Stranders GA, Wyllie AL, et al. Development of the nasopharyngeal microbiota in infants with cystic fibrosis. Am J Respir Crit Care Med. 2016;193(5):504–15.
411. Renwick J, McNally P, John B, DeSantis T, Linnane B, Murphy P, et al. The microbial community of the cystic fibrosis airway is disrupted in early life. PLoS One. 2014;9(12):e109798.
412. Blainey PC, Milla CE, Cornfield DN, Quake SR. Quantitative analysis of the human airway microbial ecology reveals a pervasive signature for cystic fibrosis. Sci Transl Med. 2012;4(153):153ra30.
413. Zemanick ET, Wagner BD, Robertson CE, Stevens MJ, Szefler SJ, Accurso FJ, et al. Assessment of airway microbiota and inflammation in cystic fibrosis using multiple sampling methods. Ann Am Thorac Soc. 2015;12(2):221–9.
414. Boutin S, Graeber SY, Weitnauer M, Panitz J, Stahl M, Clausznitzer D, et al. Comparison of microbiomes from different niches of upper and lower airways in children and adolescents with cystic fibrosis. PLoS One. 2015;10(1):e0116029.

415. Rogers GB, Carroll MP, Serisier DJ, Hockey PM, Jones G, Kehagia V, et al. Use of 16S rRNA gene profiling by terminal restriction fragment length polymorphism analysis to compare bacterial communities in sputum and mouthwash samples from patients with cystic fibrosis. J Clin Microbiol. 2006;44(7):2601–4.
416. Brown PS, Pope CE, Marsh RL, Qin X, McNamara S, Gibson R, et al. Directly sampling the lung of a young child with cystic fibrosis reveals diverse microbiota. Ann Am Thorac Soc. 2014;11(7):1049–55.
417. Dickson RP, Erb-Downward JR, Freeman CM, McCloskey L, Falkowski NR, Huffnagle GB, et al. Bacterial topography of the healthy human lower respiratory tract. MBio. 2017;8(1):e02287–16.
418. Bassis CM, Erb-Downward JR, Dickson RP, Freeman CM, Schmidt TM, Young VB, et al. Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. MBio. 2015;6(2):e00037.
419. Charlson ES, Bittinger K, Haas AR, Fitzgerald AS, Frank I, Yadav A, et al. Topographical continuity of bacterial populations in the healthy human respiratory tract. Am J Respir Crit Care Med. 2011;184(8):957–63.
420. Charlson ES, Bittinger K, Chen J, Diamond JM, Li H, Collman RG, et al. Assessing bacterial populations in the lung by replicate analysis of samples from the upper and lower respiratory tracts. PLoS One. 2012;7(9):e42786.
421. Nguyen LD, Viscogliosi E, Delhaes L. The lung mycobiome: an emerging field of the human respiratory microbiome. Front Microbiol. 2015;6:89.
422. Bousbia S, Papazian L, Saux P, Forel JM, Auffray JP, Martin C, et al. Repertoire of intensive care unit pneumonia microbiota. PLoS One. 2012;7(2):e32486.
423. McTaggart LR, Copeland JK, Surendra A, Wang PW, Husain S, Coburn B, et al. Mycobiome sequencing and analysis applied to fungal community profiling of the lower respiratory tract during fungal pathogenesis. Front Microbiol. 2019;10:512.
424. Bittinger K, Charlson ES, Loy E, Shirley DJ, Haas AR, Laughlin A, et al. Improved characterization of medically relevant fungi in the human respiratory tract using next-generation sequencing. Genome Biol. 2014;15(10):487.
425. Charlson ES, Diamond JM, Bittinger K, Fitzgerald AS, Yadav A, Haas AR, et al. Lung-enriched organisms and aberrant bacterial and fungal respiratory microbiota after lung transplant. Am J Respir Crit Care Med. 2012;186(6):536–45.
426. Cui L, Lucht L, Tipton L, Rogers MB, Fitch A, Kessinger C, et al. Topographic diversity of the respiratory tract mycobiome and alteration in HIV and lung disease. Am J Respir Crit Care Med. 2015;191(8):932–42.
427. Halwachs B, Madhusudhan N, Krause R, Nilsson RH, Moissl-Eichinger C, Hogenauer C, et al. Critical issues in mycobiota analysis. Front Microbiol. 2017;8:180.
428. Krause R, Halwachs B, Thallinger GG, Klymiuk I, Gorkiewicz G, Hoenigl M, et al. Characterisation of candida within the mycobiome/microbiome of the lower respiratory tract of ICU patients. PLoS One. 2016;11(5):e0155033.
429. Krause R, Moissl-Eichinger C, Halwachs B, Gorkiewicz G, Berg G, Valentin T, et al. Mycobiome in the lower respiratory tract - a clinical perspective. Front Microbiol. 2016;7:2169.
430. Fraczek MG, Chishimba L, Niven RM, Bromley M, Simpson A, Smyth L, et al. Corticosteroid treatment is associated with increased filamentous fungal burden in allergic fungal disease. J Allergy Clin Immunol. 2018;142(2):407–14.
431. Young JC, Chehoud C, Bittinger K, Bailey A, Diamond JM, Cantu E, et al. Viral metagenomics reveal blooms of anelloviruses in the respiratory tract of lung transplant recipients. Am J Transplant. 2015;15(1):200–9.
432. Lewandowska DW, Schreiber PW, Schuurmans MM, Ruehe B, Zagordi O, Bayard C, et al. Metagenomic sequencing complements routine diagnostics in identifying viral pathogens in lung transplant recipients with unknown etiology of respiratory infection. PLoS One. 2017;12(5):e0177340.
433. Langelier C, Zinter MS, Kalantar K, Yanik GA, Christenson S, O'Donovan B, et al. Metagenomic sequencing detects respiratory pathogens in hematopoietic cellular transplant patients. Am J Respir Crit Care Med. 2018;197(4):524–8.
434. Zinter MS, Dvorak CC, Mayday MY, Iwanaga K, Ly NP, McGarry ME, et al. Pulmonary metagenomic sequencing suggests missed infections in immunocompromised children. Clin Infect Dis. 2019;68(11):1847–55.
435. Mitchell AB, Oliver BG, Glanville AR. Translational aspects of the human respiratory virome. Am J Respir Crit Care Med. 2016;194(12):1458–64.
436. Yang J, Yang F, Ren L, Xiong Z, Wu Z, Dong J, et al. Unbiased parallel detection of viral pathogens in clinical samples by use of a metagenomic approach. J Clin Microbiol. 2011;49(10):3463–9.
437. Wylie KM, Mihindukulasuriya KA, Sodergren E, Weinstock GM, Storch GA. Sequence analysis of the human virome in febrile and afebrile children. PLoS One. 2012;7(6):e27735.
438. Zoll J, Rahamat-Langendoen J, Ahout I, de Jonge MI, Jans J, Huijnen MA, et al. Direct multiplexed whole genome sequencing of respiratory tract samples reveals full viral genomic information. J Clin Virol. 2015;66:6–11.
439. Wang Y, Zhu N, Li Y, Lu R, Wang H, Liu G, et al. Metagenomic analysis of viral genetic diversity in respiratory samples from children with severe acute respiratory infection in China. Clin Microbiol Infect. 2016;22(5):458 e1–9.
440. Zhou Y, Fernandez S, Yoon IK, Simasathien S, Watanaveeradej V, Yang Y, et al. Metagenomics study of viral pathogens in undiagnosed respiratory specimens and identification of human enteroviruses at a Thailand Hospital. Am J Trop Med Hyg. 2016;95(3):663–9.

Bronchoalveolar Lavage: Biomarkers

10

Nicolaus Schwerk and Hartmut Grasemann

Paediatric flexible bronchoscopy represents an established diagnostic and therapeutic procedure in children and adolescents with congenital and acquired respiratory diseases. Besides the visual evaluation of the entire assessable respiratory tract enabling the investigating pulmonologist to detect structural and/or functional upper and lower airways abnormalities, bronchoalveolar lavage (BAL) is used to recover cellular and non-cellular components from the bronchial and alveolar air spaces. BAL is routinely used for the analysis of the cellular composition of the luminal airway secretions or epithelial lining and, specifically in children unable to expectorate sputum, for microbiology testing. Differential counts of the cellular composition of the recovered BAL fluid (BALF), can provide important information about the presence and kind of inflammatory response (e.g. lymphocytic vs. neutrophilic), but is usually not diagnostic for specific conditions (Table 10.1). Beyond routine cytology, specific methods of detecting or quantifying cellular and non-cellular BALF compounds, which can be summarized as 'biomarkers', are therefore helpful for the diagnosis of specific conditions, the evaluation of treatment response and also for research purposes. A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic response to a therapeutic intervention' [1]. Some BALF biomarkers are currently used for diagnostic purposes in clinical practice (Table 10.2). An increasing number of biomarkers has also been used in clinical studies on different lung diseases, for instance

Table 10.1 Routine variables measured in BALF

Variables	Comments
Recovery	Acceptable quality if recovery is >40%
Numbers of cells	Not performed in all centres. Normal range: 10–60 × 10^4/ml
Differential cell count	Macrophages, polymorphonuclear neutrophils (PMNs), lymphocytes. Contamination with epithelial cells is an indicator of a poor quality BAL
Microbiological testing	Samples must be collected in sterile containers and processed as soon as possible to avoid contamination
Virology testing	In some centres also used in routine diagnostics

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_10

Table 10.2 Established biomarkers in specific respiratory conditions

Condition	Biomarker	Comments
Chronic pulmonary aspiration	Lipid staining (e.g. Sudan)	Lipid-laden macrophages are suggestive of but not diagnostic for aspiration
Alveolar haemorrhage	Hemosiderin staining	Hemosiderin-laden macrophages are suggestive of but not diagnostic for alveolar haemorrhage
Alveolar proteinosis	Periodic acid-Schiff-staining (PAS)	PAS-positive non-cellular material is suggestive of but not diagnostic for pulmonary alveolar proteinosis (e.g. may also be positive in glycogen storage diseases)
Surfactant disorders	Surfactant analysis	When inherited surfactant protein deficiencies (e.g. SPB, SPC, and ABCA3) or other causes of pulmonary alveolar proteinosis are suspected
Langerhans histiocytosis	CD1a	Detection of 5% CD1a-positive cells is diagnostic for pulmonary histiocytosis
Hypersensitivity pneumonitis	CD4/CD8 ratio	CD4/CD8-ratios when hypersensitivity pneumonitis or sarcoidosis is suspected (in children it is neither specific nor sensitive)

in cystic fibrosis (CF) [2–6]. This chapter provides an overview of already established biomarkers used in clinical practice but also discusses some potential useful biomarkers in specific disease entities.

Biomarkers for Specific Conditions

Pulmonary Langerhans Cell Histiocytosis

Even though radiologic findings in children with pulmonary Langerhans cell histiocytosis (PLCH) are typically showing pulmonary bilateral, diffuse and cystic lesions of various sizes with or without concurrent pneumothorax, confirmation of PLCH can be very challenging, especially in critically ill children. Lung biopsy remains the gold standard for diagnosis but might be complicated by severe and persisting pneumothoraces. Bronchoscopy with BAL is therefore recommended as a less invasive procedure to confirm the diagnosis. Detection of 5% CD1a-positive cells in BALF is diagnostic for PLCH [7].

Hypersensitivity Pneumonitis

In patients with subacute or chronic hypersensitivity pneumonitis (HP) a predominant lymphocytic alveolitis is present in most cases. In adults this is classically delineated by an increase of CD8+ lymphocytes in BALF, with an inversion of the CD4+/CD8+ ratio. Therefore, a CD4+/CD8+ ratio <0.8 is considered to be suggestive for HP in adults even though a relevant proportion of false-negative results has been described [8]. In children with suspected HP, the CD4+/CD8+ ratio seems not to be a valuable biomarker for the diagnosis of HP. In one study of nine children with acute HP, no decreased CD4+/CD8+ ratio was observed in the presence of lymphocytic alveolitis in any of these patients [9].

Cystic Fibrosis

Established inflammatory markers in BALF from patients with cystic fibrosis (CF) include total and differential polymorphonuclear (PMN) neutrophil count, elastase and its complexes with inhibitors (e.g. neutrophil elastase (NE)-a1-antitrypsin) and the inflammatory cytokines interleukin (IL)-8, IL-6 and tumour necrosis factor (TNF)-a. Spontaneously expectorated or induced sputum is typically used to measure biomarkers of lung inflammation or infection in CF. However, early therapeutic interventions can improve long-term outcomes, but younger CF patients are often not able to produce sputum. BALF has the potential to provide biomarkers of early disease processes in infants and children with CF that can be used to guide therapy. An example for such a BALF bio-

marker in infants is free neutrophil elastase that was shown to predict the development of persistent bronchiectasis at 1 and 3 years, when present in BALF at 3 months of age [10]. In longitudinal studies in CF infants, the acquisition of bacterial infection was accompanied by a two-fold increase in BALF PMN cell count, neutrophil elastase and IL-8 levels, while eradication of infection resulted in a sustained reduction in neutrophil elastase and IL-8, as demonstrated in repeat BAL performed up to 18 months [11, 12]. A significant decrease in PMN cell counts, neutrophil elastase and IL-8 levels was also seen in children with CF treated with inhaled rhDNase, a therapy that results in improved pulmonary function [13]. An interesting area of active research is the quantification of metabolites in biological samples from CF patients using sensitive methods for detection such as mass spectrometry. The purine metabolites hypoxanthine and xanthine as well as a number of amino acids were found to be elevated in BALF of children with CF, and correlated with neutrophil counts and measures of pulmonary function [14].

Chronic Lung Allograft Dysfunction and Acute Cellular Rejection

Increased BALF neutrophil counts, in the range of 20% or greater, predict future bronchiolitis obliterans (BOS) [15–17]. In addition, analyses of lymphocyte subpopulations in BOS have revealed that while the levels of total lymphocytes, CD4+ cells and CD8+ cells have only weak associations with BOS, FOXP3 + CD4+ T-regulatory (T-reg) cells and CCR7+ T-regs are significantly reduced in the BALF from lung transplant recipients with BOS. A low proportion (less than 3.2%) of T-regs has been shown to predict the development of BOS within 2 years post-transplant [18, 19]. Several soluble BAL parameters, including interleukin-8, alpha defensins and matrix metalloproteinase (MMP-9), have also been shown to be associated with BOS and may help to distinguish different forms of acute lung allograft rejection [20]. Studies of biomarkers in acute cellular rejection (ACR) show inconsistent results but suggest that an increase in IL-1, IL-6, IL-15, IL-17 or CXCL10 in BALF might warrant suspicion for ACR [21].

References

1. Lesko LJ, Atkinson AJ Jr. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. Annu Rev Pharmacol Toxicol. 2001;41:347–66.
2. Fayon M, Kent L, Bui S, Dupont L, Sermet I, European Cystic Fibrosis Society Clinical Trial Network Standardisation Committee. Clinimetric properties of bronchoalveolar lavage inflammatory markers in cystic fibrosis. Eur Respir J. 2014;43(2):610–26.
3. Corwin RW, Irwin RS. The lipid-laden alveolar macrophage as a marker of aspiration in parenchymal lung disease. Am Rev Respir Dis. 1985;132(3):576–81.
4. Furuya ME, Moreno-Cordova V, Ramirez-Figueroa JL, Vargas MH, Ramon-Garcia G, Ramirez-San Juan DH. Cutoff value of lipid-laden alveolar macrophages for diagnosing aspiration in infants and children. Pediatr Pulmonol. 2007;42(5):452–7.
5. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. Pediatr Pulmonol. 1999;27(6):419–22.
6. De Baets F, Aarts C, Van Daele S, Haerynck F, De Wachter E, De Schutter I, et al. Milk protein and Oil-Red-O staining of alveolar macrophages in chronic respiratory disease of infancy. Pediatr Pulmonol. 2010;45(12):1213–9.
7. Refabert L, Rambaud C, Mamou-Mani T, Scheinmann P, de Blic J. Cd1a-positive cells in bronchoalveolar lavage samples from children with Langerhans cell histiocytosis. J Pediatr. 1996;129(6):913–5.
8. Caillaud DM, Vergnon JM, Madroszyk A, Melloni BM, Murris M, Dalphin JC, et al. Bronchoalveolar lavage in hypersensitivity pneumonitis: a series of 139 patients. Inflamm Allergy Drug Targets. 2012;11(1):15–9.
9. Ratjen F, Costabel U, Griese M, Paul K. Bronchoalveolar lavage fluid findings in children with hypersensitivity pneumonitis. Eur Respir J. 2003;21(1):144–8.
10. Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, et al. Risk factors for bronchiectasis in children with cystic fibrosis. N Engl J Med. 2013;368(21):1963–70.
11. Armstrong DS, Grimwood K, Carlin JB, et al. Lower airway inflammation in infants and young children with cystic fibrosis. Am J Respir Crit Care Med. 1997;156:1197–204.
12. Armstrong DS, Hook SM, Jamsen KM, et al. Lower airway inflammation in infants with cystic fibrosis detected by newborn screening. Pediatr Pulmonol. 2005;40:500–10.

13. Paul K, Rietschel E, Ballmann M, et al. Effect of treatment with dornase alpha on airway inflammation in patients with cystic fibrosis. Am J Respir Crit Care Med. 2004;169:719–25.
14. Esther CR Jr, Coakley RD, Henderson AG, Zhou YH, Wright FA, Boucher RC. Metabolomic evaluation of neutrophilic airway inflammation in cystic fibrosis. Chest. 2015;148(2):507–15.
15. Reynaud-Gaubert M, Marin V, Thirion X, et al. Upregulation of chemokines in bronchoalveolar lavage fluid as a predictive marker of post-transplant airway obliteration. J Heart Lung Transplant. 2002;21:721–30.
16. Reynaud-Gaubert M, Thomas P, Badier M, Cau P, Giudicelli R, Fuentes P. Early detection of airway involvement in obliterative bronchiolitis after lung transplantation. Functional and Bronchoalveolar lavage cell findings. Am J Respir Crit Care Med. 2000;161:1924–9.
17. Slebos DJ, Postma DS, Koeter GH, Van Der Bij W, Boezen M, Kauffman HF. Bronchoalveolar lavage fluid characteristics in acute and chronic lung transplant rejection. J Heart Lung Transplant. 2004;23:532–40.
18. Bhorade SM, Chen H, Molinero L, et al. Decreased percentage of CD4+FoxP3+ cells in bronchoalveolar lavage from lung transplant recipients correlates with development of bronchiolitis obliterans syndrome. Transplantation. 2010;90:540–6.
19. Gregson AL, Hoji A, Palchevskiy V, et al. Protection against bronchiolitis obliterans syndrome is associated with allograft CCR7+ CD45RA- T regulatory cells. PLoS One. 2010;5:e11354.
20. Kennedy VE, Todd JL, Palmer SM. Bronchoalveolar lavage as a tool to predict, diagnose and understand bronchiolitis obliterans syndrome. Am J Transplant. 2013;13(3):552–61.
21. Speck NE, Schuurmans MM, Benden C, Robinson CA, Huber LC. Plasma and bronchoalveolar lavage samples in acute lung allograft rejection: the potential role of cytokines as diagnostic markers. Respir Res. 2017;18(1):151.

11 Anesthesia Consideration for Flexible Bronchoscopy

Benjamin B. Bruins, Elizabeth K. Laverriere, and Todd J. Kilbaugh

Goals of an Airway Anesthesia Team

Patients presenting for flexible bronchoscopy frequently have the expectation that the procedure will be done under conditions of general anesthesia. Working with an anesthesia team provides several advantages for patient safety, most notably a team dedicated solely to patient monitoring, allowing the bronchoscopist to concentrate on the task at hand.

Shared Goals for Airway Anesthesia Team

1. Expectation setting for the optimal patient experience
2. Adequate oxygenation and perfusion to avoid end-organ ischemic injury
3. Establishment of optimal conditions for airway assessment
4. Rapid recovery to preprocedural status

Preoperative Assessment

The perioperative team should ensure that a comprehensive history and physical exam are completed before embarking on induction of anesthesia. External airway evaluation should include an assessment of the size of oral aperture, relative size of tongue, inter-incisor distance, mento-hyoid distance, active range of motion of the neck, and quality of dentition. Additionally, nil per os time and aspiration risk should be evaluated and optimal timing of induction should be established to limit the risk of aspiration. If available, previous anesthesia and sedation history may help elucidate prior untoward events and allow for alternative planning to mitigate these risks from recurring. Furthermore, presenting signs and symptomatology are important to discuss with the patient, family, and medical teams, including current respiratory support, severity of respiratory embarrassment, and extrapulmonary comorbid conditions.

Preoperative Preparation

Procedural success is contingent upon communication and preparation. Imperative team conversations include the specific goals of the procedure and selection of ideal location. It is helpful for the bronchoscopist and anesthesiologist to discuss the aspects of airway anatomy that need to be evalu-

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ated, the need for bronchoalveolar lavage, and the need for dynamic airway evaluation. Critically ill patients with significant lung disease may benefit avoiding transportation and completing the procedure in the intensive care unit, while others will benefit from the additional space, equipment, and expertise that can be provided in an operative theater. Regardless of the locale, standard American Society of Anesthesiologists monitors should be available including continuous electrocardiogram, noninvasive blood pressure, pulse oximetry, temperature, and end tidal carbon dioxide monitoring [1]. Additional monitoring such as processed electroencephalography [2] or near infrared spectroscopy [3] has proven to have limited benefit, especially in pediatrics, but can be used in selected scenarios. It is crucial that emergency medications and tools be available during all phases of the process. An assortment of airway equipment should be available, including anesthesia masks, laryngeal mask airways (LMA), oral and nasal pharyngeal airways, and endotracheal tubes (ETT). Emergency medications should include Pediatric Advanced Life Support (PALS) [4] specific drugs such as epinephrine and atropine as well as agents to treat laryngospasm such as propofol and succinylcholine.

Induction and Maintenance of Anesthesia

After the preoperative discussion between bronchoscopist and anesthesiologist, anesthesia can be induced to achieve the predetermined goals. While there are many approaches to plan and execute an appropriate anesthetic, there are several overarching themes that are helpful to discuss. The first is whether there is a need to have the patient maintain spontaneous respiration. This is often necessary for dynamic airway assessment to evaluate for vocal cord mobility and airway malacia, but carries an increased risk of bronchospasm, laryngospasm, and hypotension. The second theme involves the need to have an unaltered airway to evaluate. Anesthesiologists frequently relieve glossoptosis with the jaw thrust maneuver, bypass upper airway obstruction with airway adjuncts, and provide airway pressure to distend collapsible airways. These routine practices for an anesthesiologist to minimize airway obstruction may adversely affect the diagnostic quality of the bronchoscopy. The goal should be to allow rapid assessment of the airway while providing optimal oxygenation, sometimes tolerating periods of hypercapnia if hemodynamics are not affected and these effects are not seen as detrimental to intracranial physiology. As such, special care should be taken to avoid this in patients with intracranial and pulmonary hypertension [5], as hypercarbia may lead to worsening of their underlying pathophysiologic process.

Design of an optimal anesthetic plan may involve more than one airway plan. The authors frequently utilize the following plan to minimize patient risks, while providing optimal conditions for a complete bronchoscopy. Initially, spontaneous respiration is maintained while oxygen is provided with a facemask via the anesthesia circuit without positive end-expiratory pressure (PEEP) or maneuvers to relieve upper airway obstruction, and bronchoscopy is performed through an adaptor attached to the mask. Upon completion of the evaluation of the supraglottic airway, an LMA is placed while the patient is still spontaneously ventilating without PEEP for dynamic lower airway evaluation. Controlled ventilation with PEEP is then used to clear carbon dioxide and re-recruit atelectatic lung units during the bronchoalveolar lavage portion of the examination. In the setting of hypoxemia – an ETT may be utilized to allow for additional mean airway pressure delivery to improve oxygenation. Frequent communication between all team members is essential to provide safe management of the patient while also allowing for optimal conditions for the diagnostic procedure. It is not uncommon for multiple airway plans to be utilized, and for the plan to change based on the patient's response to the anesthetic. Preparation and communication are key.

Regardless of the initial airway plan, all team members should work to optimize oxygenation. This allows for additional patient safety, and also eliminates the need for pauses in the procedure

due to oxyhemoglobin desaturation. Oxygen can easily be administered by the bronchoscopist through the working channel in the patient with a patent airway. Alternatively, passive oxygenation can be administered via anesthesia mask, nasal cannula, or an endotracheal tube insufflating in the pharynx. Patients at higher risk of oxyhemoglobin desaturation may benefit from controlled or assisted ventilation with oxygen delivery via LMA or ETT. LMAs are typically sized according to patient weight, and offer a conduit of adequate size for the bronchoscopy in almost all situations. Conversely, the external diameter of the bronchoscope can exceed the inner diameter of an age-appropriate ETT. A discussion regarding relative risks of ETT size versus scope downsizing is important in the optimal selection of ETT.

The selection of pharmacologic agents requires a working knowledge of the available agents and their relative benefits. Agents should provide analgesia, amnesia, areflexia, and akinesis. Below each agent will be discussed as a brief review.

Inhalational agents (volatile anesthetics such as sevoflurane) are a widely used class of medications which are delivered through specialized equipment. They have a reliable dose-response curve and can even be administered before intravenous access is obtained (inhaled delivery). To limit environmental contamination, these agents are best administered when the respiratory circuit has minimal leak. Additionally, a patent airway with continuous administration of volatile anesthetic is important to maintain a desired depth of anesthesia. Sevoflurane has smooth muscle relaxant effects that can be used in the setting of refractory bronchoconstriction. Lower doses of sevoflurane are needed to produce unconsciousness than those that are needed to prevent movement such as coughing. Vasodilation is commonly seen with use of volatile anesthetics and is directly related to the dose administered. Sevoflurane may be used as a sole agent for bronchoscopy but significant doses are needed to prevent airway reflexes and movement, necessitating close monitoring of hemodynamics. Volatile anesthetics are also known to be triggering agents for malignant hyperthermia, and should not be used in patients known or suspected to be at risk.

Propofol is a commonly used anesthetic agent that is delivered via intravenous route. Bolus doses of propofol are associated with rapid induction of unconsciousness, and if used for short procedures, they are associated with a rapid recovery of consciousness. The intravenous administration can be associated with pain at the injection site, which is mitigated with administration analgesics or intravenous lidocaine or delivery of the medication in a larger vein. Propofol does not have analgesic properties when used as a sole agent. Vasodilation and hypotension are also commonly seen with propofol administration and are directly related to dose administered. Much like sevoflurane, propofol can be used as a sole agent for bronchoscopy but significant doses are needed to prevent airway reflexes and movement, necessitating close monitoring of hemodynamics.

Dexmedetomidine is intravenous alpha agonist which is typically inadequate as a sole agent for bronchoscopy but can be a valuable adjunctive medication. It is thought to preserve respiratory drive even at high doses. Administration of dexmedetomidine can significantly reduce the dose requirements of other agents needed for ideal procedural conditions. As an alpha-agonist it can induce significant bradycardia and at higher doses, hypertension. These responses are especially seen with loading doses of the medication [6]. Maintenance infusions can be associated with hypotension.

Ketamine is a dissociative anesthetic, antagonizing the N-methyl-D-aspartate (NMDA) receptor. It provides quality analgesia and amnesia as a sole agent or in combination with others. It has sympathomimetic effects which result in hemodynamic stability and are likely responsible for the bronchodilation which has been described with its use. Especially in older children, associated emergence hallucinations can be unpleasant, and warrant concomitant use of other agents. The use of ketamine is also associated with salivation, often prompting the use of anti-sialagogues.

Short-acting opioids such as fentanyl or remifentanil do not produce amnesia and so should

not be used as sole agents. Opioids reduce airway reactivity, allowing for optimal bronchoscopy conditions in the nonparalyzed patient, and provide antitussive effects during emergence. Opioids cause dose-related respiratory depression, so careful titration of dosage is required when spontaneous breathing is desired. Larger doses often necessitate controlled ventilation. Opioids also significantly reduce the dosage of other agents needed, limiting hemodynamic changes in the periprocedural period.

Neuromuscular blocking agents provide akinesis, but do not provide amnesia or analgesia, so should not be used as sole agents. The use of neuromuscular blockade nearly eliminates the risk of laryngospasm and allows dose reduction of other agents, allowing for improved hemodynamic profiles. Use of neuromuscular blockade is contraindicated if vocal cord motion, dynamic airway collapse, or other spontaneous breathing respiration assessments are needed.

Perioperative Events

Preparation for common intraoperative events can lead to rapid identification and treatment, ensuring optimal patient safety. The most common adverse events include hypoxemia and hypotension and can be multifactorial in their etiologies.

Hypoxemia is exceedingly common in patients undergoing bronchoscopy. Hypoventilation from respiratory depressant effects of anesthetic medications or from airway obstruction is commonly noted. Laryngospasm and bronchospasm are frequently noted airway reflexes that result in dynamic airway obstruction, and typically resolve with deepening of the anesthetic. Alternatively, ventilation and perfusion can become mismatched, especially after bronchoalveolar lavage or atelectasis from derecruitment of lung units in the supine position. This can be exacerbated by anesthetic blunting of the normal hypoxic pulmonary vasoconstriction and may be responsive to recruitment maneuvers.

Hypotension is an expected but undesirable side effect of many of the anesthetic drugs used for bronchoscopy. This can be exacerbated by medical comorbidities including preoperative diuresis, myocardial dysfunction, or sepsis. The preoperative assessment must include an estimation of intravascular volume and cardiac output – with contingency plans to augment preload, cardiac function, and systemic vascular resistance as needed for stable hemodynamics. This requires adequate intravenous access and may require pre-operative optimization of fluid status before induction of anesthesia. In most cases, it is helpful to have immediate access to vasoconstrictors and inotropes to optimize organ perfusion throughout the procedure.

Other life-threatening events are thankfully less common. Despite this, it is imperative for the anesthesiologist to have a working knowledge of all PALS algorithms and access to resuscitation equipment in the event of patient deterioration.

Recovery and Postoperative Care

Emergence is the cessation of anesthesia and the transition to postoperative care. This is often more challenging than the process of induction and requires significant vigilance on the part of the anesthesia team. Of utmost importance is selection of the patient who will require postoperative ventilator support for which emergence is inappropriate (Fig. 11.1).

Patients on baseline noninvasive ventilatory support can often be successfully extubated at the completion of the procedure, but every effort should be made to return to noninvasive support immediately after extubation. However, plans

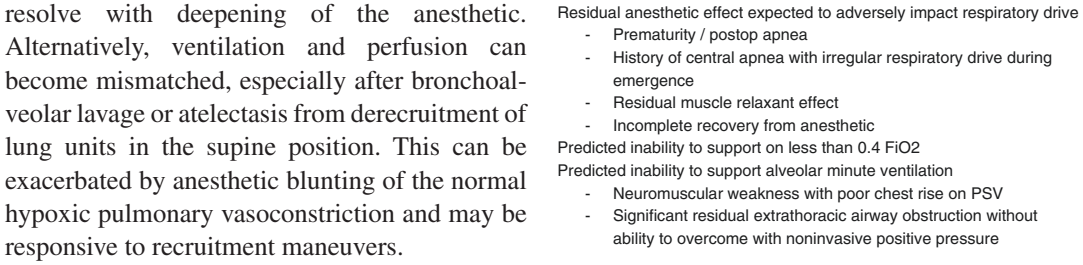

Fig. 11.1 Common indications for postoperative invasive mechanical support

should be made in case the patient requires a higher level of support following the procedure.

Removal of an LMA or ETT can occur while the patient is still under general anesthesia (deep extubation). This has the benefits of decreased coughing and increased efficiency from a room turnover standpoint. Alternatively, the LMA or ETT can be removed while the patient has recovery of protective airway reflexes (awake extubation). Awake extubation allows the practitioner to provide positive pressure throughout the emergence process, which is of particular benefit for patients with atelectasis or neuromuscular weakness.

Emergence agitation or delirium is commonly seen in pediatric patients. It consists of agitation not attributed to pain, and typically resolves after completion of emergence from anesthesia. There are many risk factors and treatment modalities that are beyond the scope of this text, but care should be taken to avoid patient self-injury during the period of emergence agitation.

Postprocedural pain is mild after most bronchoscopic procedures and is primarily attributed to sore throat. Treatment options include systemic analgesics such as nonsteroidal anti-inflammatory drugs, acetaminophen, or opioids. Alternatively, local anesthetic throat lozenges or sprays can provide pain relief. While opioids are infrequently needed for analgesia, they also offer antitussive effects which may be desirable for some patients after bronchioalveolar lavage.

Conclusion

Pediatric flexible bronchoscopy is frequently associated with administration of general anesthesia. Communication between the pediatric anesthesiologist and the proceduralist is paramount for the completion of a successful airway evaluation. Choice of anesthetic agents and airway plans is less important than the knowledge of specific advantages and disadvantages of each selection.

References

1. ASA Standards and Practice Parameters. Standards for Basic Anesthetic Monitoring: ASAHQ; [approved by the ASA House of Delegates on Oct 21, 1986, last amended Oct 20, 2010, and last affirmed on Oct 28, 2016]. Available from: https://www.asahq.org/~/media/sites/asahq/files/public/resources/standards-guidelines/standards-for-basic-anesthetic-monitoring.pdf.
2. Bannister CF, Brosius KK, Sigl JC, Meyer BJ, Sebel PS. The effect of bispectral index monitoring on anesthetic use and recovery in children anesthetized with sevoflurane in nitrous oxide. Anesth Analg. 2001;92(4):877–81.
3. Kasman N, Brady K. Cerebral oximetry for pediatric anesthesia: why do intelligent clinicians disagree? Paediatr Anaesth. 2011;21(5):473–8.
4. de Caen AR, Berg MD, Chameides L, Gooden CK, Hickey RW, Scott HF, et al. Part 12: Pediatric advanced life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132(18 Suppl 2):S526–42.
5. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015;132(21):2037–99.
6. Friesen RH, Nichols CS, Twite MD, Cardwell KA, Pan Z, Pietra B, et al. The hemodynamic response to dexmedetomidine loading dose in children with and without pulmonary hypertension. Anesth Analg. 2013;117(4):953–9.

12 The Physiological Effects of Flexible Bronchoscopy: Lessons for the Skilled Bronchoscopist

Albin Leong

Introduction

> The health and well-being of my patient will be my first consideration. —World Medical Association Declaration of Geneva, *The Physician's Pledge*

Pediatric flexible bronchoscopy (FB) is an important diagnostic and therapeutic tool for the health of children. But what are the effects of FB itself on the patient? This chapter highlights the knowledge about the physiological effects of FB. Selected representative studies will be presented. There are many interesting and useful findings that have practical significance for judicious monitoring and prevention of adverse events during FB. Thus, this information will be valuable in helping to develop a more prudent and proficient practice of FB.

The Effects of Flexible Bronchoscopy on Pulmonary Function

Placing a bronchoscope within the airway causes airway obstruction! To quantify physiological effects, pulmonary function studies have been obtained on patients and in model systems before, after, and, in some studies, during FB.

Study results in healthy controls after FB have been variable, including findings ranging from no significant effects [1, 2] to decreased pulmonary function [3]. In adult patients with asthma, Bellinger et al. reviewed prior inconsistent studies, which generally included single before and after FB lung function changes. Their recent, more comprehensive study performed serial pulmonary function measurements up to 24 hours following FB in control subjects and patients with non-severe and severe asthma. All subjects received albuterol during pulmonary function testing performed just prior to FB. Similar decreases in FEV1 and FVC were seen among the groups, with a trend of greater change associated with disease severity. The changes persisted longer in patients with severe asthma (Fig. 12.1). A subgroup of patients with asthma underwent a second FB. Those with a 14-day pretreatment with oral prednisolone experienced a faster recovery in lung function compared to controls The authors speculated that inflammation was the cause of the persistent changes in patients with severe asthma following FB [3].

In a NHLBI/NIAID workshop on investigative bronchoprovocation and bronchoscopy, a review evidenced the safety of research bronchoscopy, including bronchoalveolar lavage (BAL), bronchial biopsy with forceps, and brush biopsy in adult patients with asthma, including patients with FEV1 <50%. They also stated that "Premedication with atropine and bronchodila-

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_12

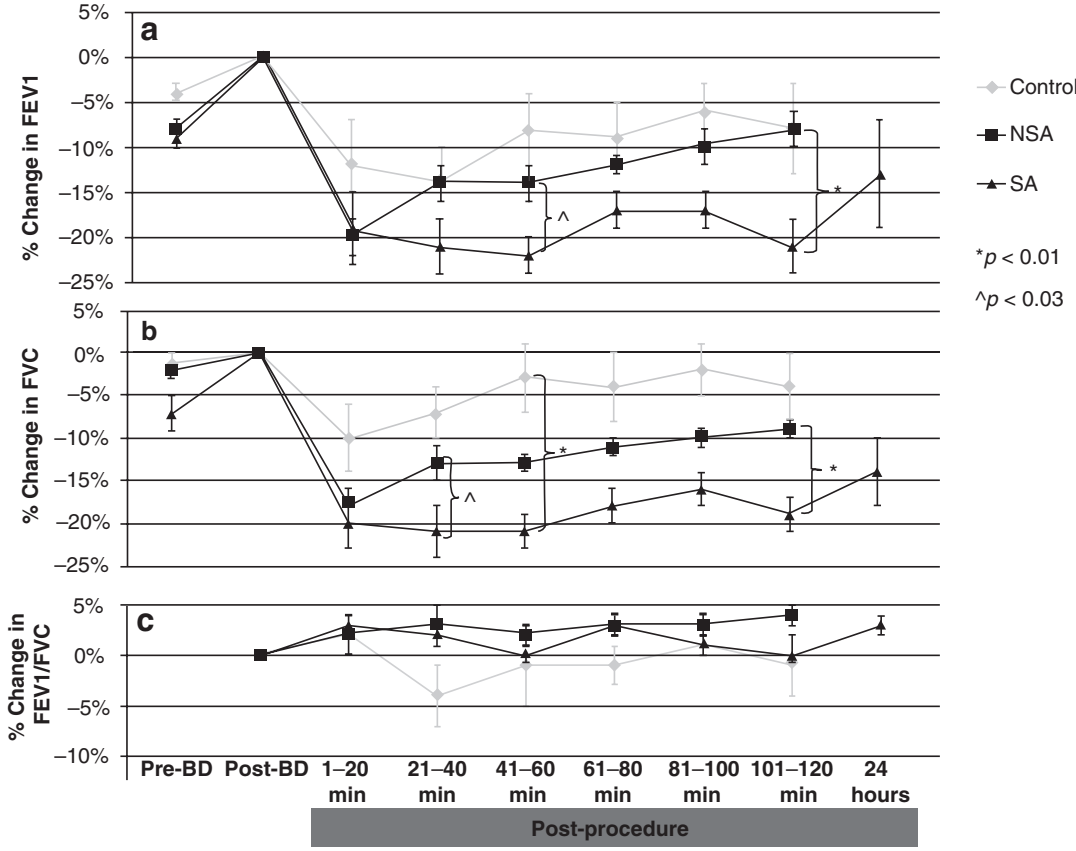

Fig. 12.1 Changes in lung function following bronchoscopy. Spirometry post-bronchoscopy was compared to the post-bronchodilator, pre-procedure spirometry (baseline). Lung function was grouped in 20-minute intervals. (A) Percent drop in FEV1 among controls, nonsevere asthma (NSA), and severe asthma (SA) patients in 20-minute intervals. At 41–60 and 101–120 minutes post-procedure, the SA group patients were significantly slower to recover lung function compared to the NSA group. Only areas of significance are noted by brackets. (B) Percent drop in FVC among controls, NSA, and SA patients in 20-minute intervals. At 21–40 minute time post-procedure, the SA group was significantly slower to recover lung function compared to the NSA. At 101–120 minute time post-procedure, SA group was significantly slower to recover lung function compared to the control group and NSA group. At 41–60 minute interval, SA had significantly lower lung function than the control group. Only areas of significance are noted by brackets. (C) Change in FEV1/FVC ratio after bronchoscopy with no significant difference in any group at any time point. (Reprinted from Bellinger et al. [3], p. 869, Copyright 2017, with permission from Taylor and Francis. www.tandfonline.com)

tors can be given or omitted, depending on the procedures to be performed and the number of bronchoscopies a research subject may safely undergo over time" [4, 5].

Matsushima et al. studied lung function measurements, including functional residual capacity (FRC), *during* FB in adults, including a subgroup of ventilated patients. Evidence of airflow obstruction peaked during FB (Fig. 12.2) [6].

Measurements of intrabronchial pressures in a prospective, randomized study of intubated adults undergoing FB showed significant increases in peak airway pressures and end-expiratory pressures in volume control (VC) mode ventilation. No changes in tidal volume, PaO_2, or $PaCO_2$ were noted. In pressure control (PC) mode, peak airway pressures were unchanged, but tidal volumes decreased significantly while end-expiratory airway pressures (though less change than the volume control mode group) and $PaCO_2$ increased. No significant changes in oxygenation were noted. Thus, while VC mode maintained tidal

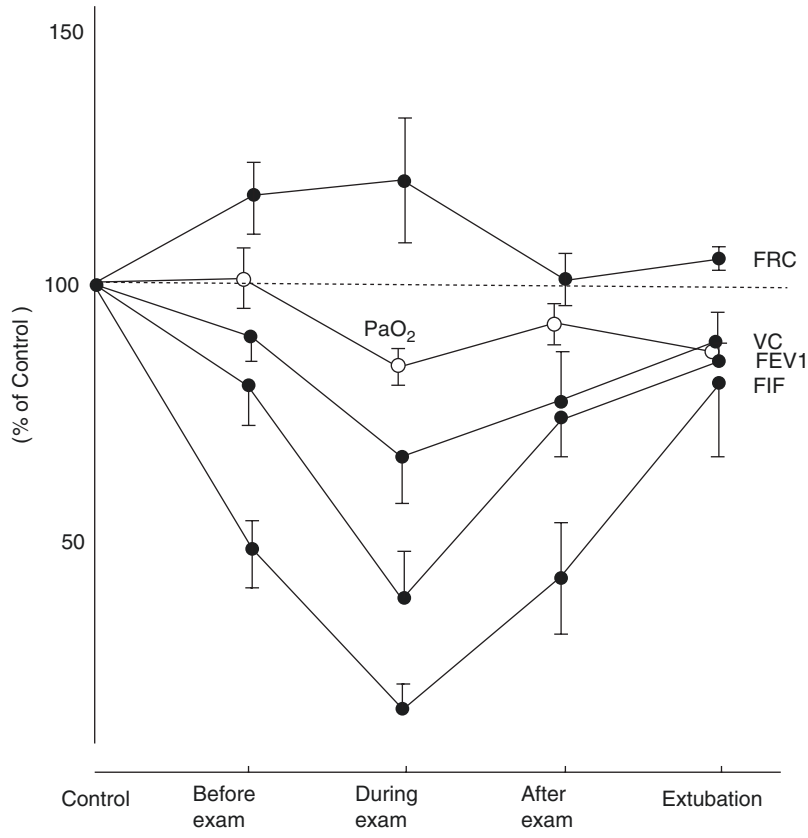

Fig. 12.2 Changes in pulmonary function and blood gases during FFB examination through an 8-mm endotracheal tube in five patients. Values are mean ± 1 SEM. (Reprinted from Matsushima et al. [6], p. 186, with permission from Elsevier)

volumes and ventilation in these patients, significant airway pressures developed [7].

Lindholm et al. likewise noted significant development of incomplete expiration (auto-PEEP) during FB in ventilated patients in VC mode, leading to a recommendation to discontinue PEEP during VC ventilation while doing FB [8]. Using an adult lung model, Lawson et al. similarly observed auto-PEEP with insertion of the bronchoscope, also less in PC than VC mode. However, they found that adjusting respiratory rates and flow patterns could minimize auto-PEEP [9].

To further analyze lung function effects of FB during mechanical ventilation, Lindholm et al. also performed experimental studies in dogs. Elevated peak end expiratory and peak pressures along with decreased tidal volumes were greatest as the bronchoscope was placed in the airways. These effects became even more pronounced in narrower endotracheal tubes. Furthermore, they measured the effect of suctioning and consequent air removal in rapidly decreasing airway pressure to a negative measurement despite ongoing mechanical ventilation (Fig. 12.3). Analogous effects were noted in a small group of ventilated adult patients with increasing $PaCO_2$ and cardiac output with decreasing tidal volume and PaO_2 during FB with "intermittent suctioning"(Fig. 12.4). As a result, one of the study conclusions included the caution to "suction for short periods only" [8].

Moreover, studies in both a lung model and ventilated adult patients revealed that suction pressures of −20 to −80 KPa can lower lung volumes by exceeding minute ventilation and thus pose a risk for lung collapse [10]. Indeed, a case report concluded that unilateral pulmonary edema was caused by negative pressure from suctioning in an infant undergoing FB [11]. Thus, the wary bronchoscopist should take precautions during FB to avoid reduction of FRC and consequent effects on gas exchange by overly zealous suctioning.

Using a smaller bronchoscope can substantially decrease the respiratory and hemodynamic effects of FB as noted in a comparison study of

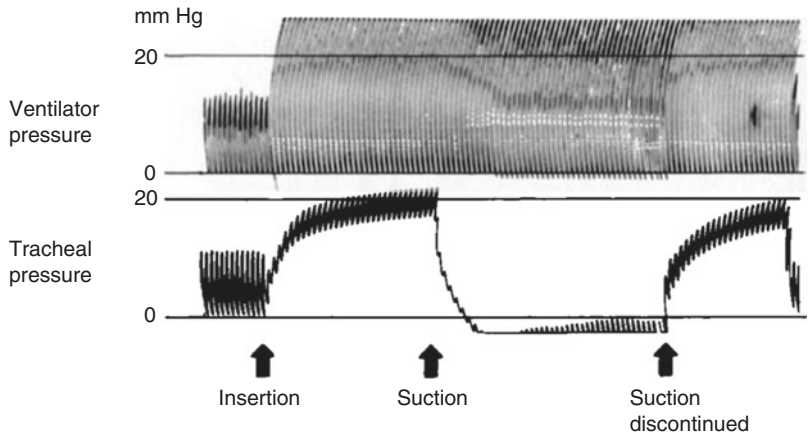

Fig. 12.3 Simultaneous recording of ventilator and intratracheal pressure in a dog during controlled mechanical ventilation through a tracheal tube of 7.0 mm ID with a tidal volume of 30 ml/kg body weight and ventilator rate of 30 cycles/min. Insertion of the 5.7 mm ED bronchoscope resulted in immediate elevation of peak inspiratory ventilator pressure due to airway obstruction. Due to the narrow scale used, full deflection of the recording pen for ventilator pressure was precluded. The tracheal pressure tracing shows a more gradual elevation of peak inhalation pressure and a marked PEEP effect of 16 mm Hg, still rising when suction started after 1 minute. When a negative pressure of 62 mm Hg was applied to the suction port, in six ventilator cycles (12 seconds), the intratracheal pressure became continuously negative, indicating removal of air from the lungs in spite of unchanged ventilator function. Discontinuation of suction gradually restored presuction tracheal pressures, which finally returned to control values upon removal of bronchoscope (at the very end of the recording). (Reprinted from Lindholm et al. [8], p. 364, with permission from Elsevier)

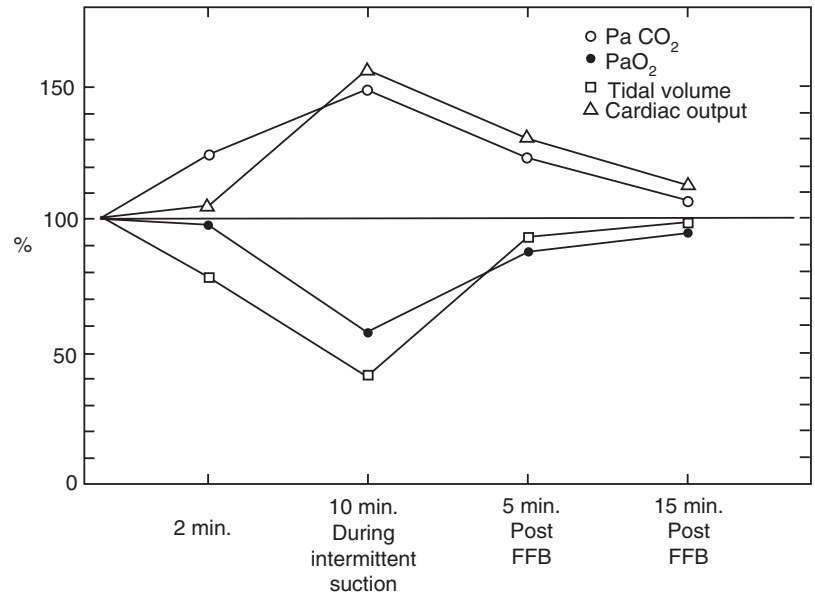

Fig. 12.4 Variation of four variables during FFB in six critically ill patients during on-going controlled mechanical ventilation. Pre-bronchoscopy values set at 100%. Measurements were repeated at 2 minutes after insertion of the bronchoscope, at 10 minutes during on-going intermittent suctioning, and at 5 and 15 minutes following FFB. (Reprinted from Lindholm et al. [8], p. 366, with permission from Elsevier)

pediatric versus adult bronchoscopes in mechanically ventilated adults undergoing BAL [12].

The underlying anatomy and respiratory physiology of infants and young children would suggest that airflow and gas exchange would be even more dramatically compromised in contrast to adults. Utilizing an ultrasonic flow sensor, spirometry during FB with a 3.5-mm bronchoscope was studied in young children 3 days to 25 months of age. The results showed significant reductions in tidal volumes (from mean 5.0 ± 0.5 to 3.4 ± 0.5 ml/kg), minute ventilation (176 ± 17 to 121 ± 13 ml/kg/min), and peak expira-

tory (78 ± 12 to 52 ± 10 ml/s) and inspiratory flows (98 ± 15 to 66 ± 12 ml/s) from passing the instrument from the hypopharynx to mid-trachea. These changes decreased with application of CPAP [13].

Hsia et al. utilized a pediatric lung model to study the potential effects of FB during mechanical ventilation in the smaller airways of children. Dramatic changes were associated with increasing size of the bronchoscope relative to the endotracheal tube. With introduction of a pediatric flexible bronchoscope during pressure control ventilation, tidal volumes decreased significantly from 700 ml to 40–280 ml (Fig. 12.5). In volume control mode, tidal volumes were generally maintained, but peak inspiratory pressures rose dramatically. In addition, with increasing obstruction from higher ratios of bronchoscope to endotracheal tube size, expiratory flows decreased and increased inadvertent or high auto-PEEP developed during volume-control ventilation, but not during pressure control ventilation. Further obstruction from intrinsic airway abnormalities as well as underlying lung disease would be expected to further amplify these results.

The authors suggested that volume-controlled ventilation would be the preferred mode for FB in ventilated patients due to better maintenance of tidal volume, but at the greater risk of developing auto-PEEP. To avoid significant obstruction and allow adequate mechanical ventilation during FB, their model suggested a diameter guideline for bronchoscope-endotracheal tube difference of >1.3 mm for infants and toddlers, >2 mm for small children, and >2.5 mm for adolescents/young adults. However, the authors acknowledged limitations to these guidelines [14].

Hemodynamic Effects

The most common and evident hemodynamic effects of FB are transient sinus tachycardia or bradycardia [15, 16]. These are felt to be due to reflex sympathetic or vagal stimulation. There have been several studies using Holter monitoring to evaluate for possible arrhythmias in adults during FB, though no similar studies in children. A prevalence of minor arrhythmias ranging from

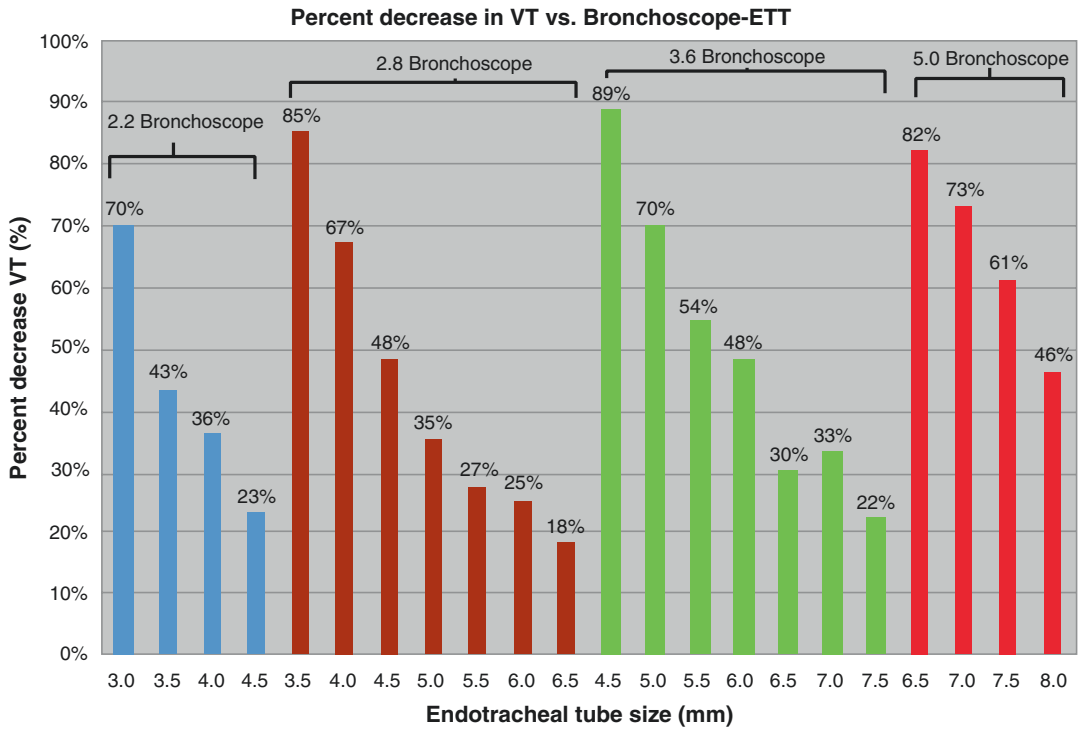

Fig. 12.5 Percent decrease in tidal volume (V_T) after bronchoscope insertion during pressure control ventilation. (Adapted from Hsia et al. [14], p. 37, with permission from Elsevier)

60% to 77%, increasing in the presence of hypoxemia, has been found in adult studies [17].

Many of the details about the stimulatory hemodynamic effects from FB have been obtained from studies in adults on FB during mechanical ventilation. These effects include increases in heart rate, mean arterial pressure, cardiac index, and pulmonary wedge pressure [8, 18, 19].

In addition, mesenteric blood flow has been discovered to be decreased during FB in adult patients undergoing FB. As a result, Nayci et al. cautioned about the potential risk of FB for mesenteric ischemia and gastrointestinal bacterial translocation [20].

In a comparison study in infants undergoing intubation by either direct laryngoscopy or fiberoptic orotracheal intubation, no significant differences in hemodynamic changes were found. Both groups experienced mildly increased heart rates and mildly decreased blood pressures along with no significant changes in oxygen saturation and end-tidal CO_2 [21].

The potential lung function effects of suctioning were previously discussed. A prospective observational study evaluating the cardiovascular effects of suctioning during endotracheal intubation in sedated children revealed transient but clinically insignificant changes in heart rate, blood pressure, cerebral regional oxygen saturation, systemic oxygen saturation, and somatic regional (renal) oxygen saturation. In addition, saline instillation during endotracheal tube suctioning had no adverse effects on systemic or cerebral oxygenation [22].

Gas Exchange Effects

The most significant physiological effect of bronchoscopy is hypoxemia due to hypoventilation and potentially due to other factors such as ventilation-perfusion inequality with bronchoalveolar lavage and depression of respiratory drive by sedation. An early study in adults using blood gas analysis revealed average declines in arterial oxygen pressure of 20 torr during the procedure with a return to baseline within 2 hours after FB [23]. As noted previously (Fig. 12.2), the peak abnormalities in gas exchange occur during the procedure. The effect of suctioning during bronchoscopy further alters gas exchange (Fig. 12.4) during mechanical ventilation, as shown in a study of adult patients on mechanical ventilation [8].

Studies in children have found that the frequency and degree of oxygen desaturation during FB is correlated with the degree of sedation, younger age (<2 years of age), and underlying laryngeal or tracheal abnormalities [16, 24].

Younger children are at greater risk for compromised ventilation from FB due to the relative size of the bronchoscope to their airways and consequent higher resistance. A study of pediatric FB utilizing pulse oximetry revealed that oxygen desaturations were frequent during FB and occurred more frequently in children who were less than 1 year of age, children with a history of prior oxygen therapy, and when the bronchoscope was located in the mid-trachea (Figs. 12.6 and 12.7). Pre-procedural assessment by pulse oximetry, supplemental oxygen, and shorter procedure time were suggested to reduce the risk of hypoxemia [24].

The evidence-based Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018 recommends, "Use supplemental oxygen during moderate procedural sedation/analgesia unless specifically contraindicated for a particular patient or procedure." Their analysis indicated that the literature was insufficient to recommend a particular method of supplemental oxygen administration. Continuous monitoring by pulse oximetry with alarms is also recommended [25].

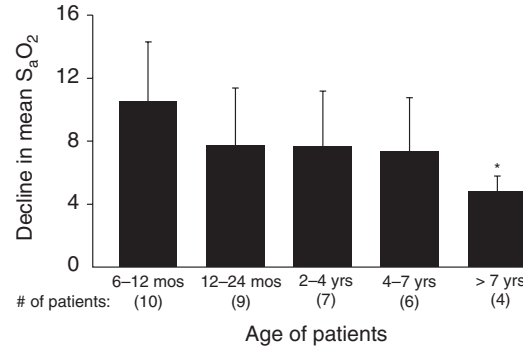

Fig. 12.6 Age of patients vs decline in mean SaO_2. Data represent percent ± SD. Asterisk indicates $p < 0.05$. (Reprinted from Schnapf [24], p. 592, with permission from Elsevier)

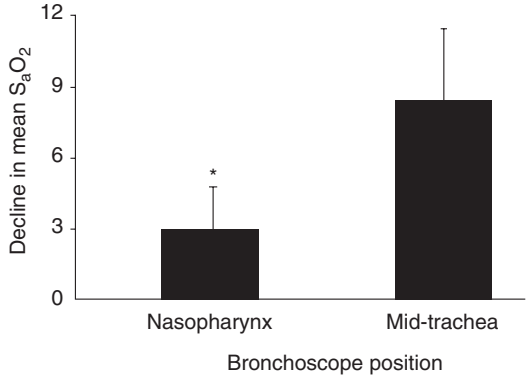

Fig. 12.7 Position of bronchoscope vs decline in mean SaO_2. Data represent percent ± SD. Asterisk indicates $p < 0.05$. (Reprinted from Schnapf [24], p. 593, with permission from Elsevier)

However, pulse oximetry monitoring does not assess potential hypoventilation. Different studies on gas exchange in FB in adults have shown variable results from no change to increased $PaCO_2$ [6, 8, 23, 26, 27].

Studies have attempted to assess potential hypercapnia in children using techniques including nasal cannula, but the accuracy of such measurements are limited during FB because of suctioning, instillation, and supplemental oxygen administration. To address the issue of more accurate $PaCO_2$ measurement during FB in children, a prospective study was performed utilizing endoscopic intratracheal CO_2. Statistically significant changes in end-tidal CO_2 (P_ECO_2) were noted in all cohorts, including those without airway lesions. The changes were greater in the cohorts with either extra-thoracic or intra-thoracic lesions (increases in P_ECO_2 of 3, 4.5, and 8 mmHg for no, extra-thoracic, intra-thoracic lesions, respectively) (Fig. 12.8) [28].

Another technique to evaluate alveolar ventilation that is not compromised by issues of alveolar plateau measurements of end-tidal CO_2 or dilution of sampled gas by instillation of fluids, suctioning, or oxygen supplementation is transcutaneous CO_2 ($TcCO_2$). Sadot et al. utilized a newer $TcCO_2$ monitor with less calibration concerns. Their study in 95 children undergoing diagnostic FB (mean duration of FB was 33 minutes) showed a median $TcCO_2$ rise of 17 mm Hg with an interquartile range of 6.5, 23.7 (Fig. 12.9). Children receiving >3.5 mg/kg of propofol (sedation to be further discussed later in this chapter) had a higher rise in $TcCO_2$ of 22.5 mmHg compared to 13.6 mmHg receiving a lower dose. Of note, they found no correlation of the peak or amount of increase of $TcCO_2$ with age, weight, bronchoscope size, or diagnosis. Moreover, they detected no differences in peak or rise of $TcCO_2$ in patients who had bronchoalveolar lavage compared to those without BAL. The authors concluded that $TcCO_2$ monitoring is feasible and should be added to FB, especially when large amounts of sedation are expected and in patients at risk for complications of respiratory acidosis [29].

Based on a meta-analysis that revealed that continuous end-tidal carbon dioxide monitoring was associated with reducing frequency of hypoxemic events, the Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018 recommended capnography "unless precluded or invalidated by the nature of the patient, procedure, or equipment" [25].

Ventilation support in order to safely perform FB may be required especially in patients with compromised lung function or airways or other significant underlying disorders. Strategies for improving oxygenation or ventilation during FB include use of supplemental oxygen with mask, nasal prongs, nasopharyngeal tube, or transnasal catheter, sedation reversal, bag-mask ventilation, CPAP via mask, laryngeal mask ventilation, including helium-oxygen, and/or intubation. However, some of these techniques will preclude a complete upper airway exam including vocal cord movement, increase the risk for laryngospasm, affect lower airway dynamics, limit the size of the bronchoscope that can be used, affect its manipulation, or require additional sedation [15, 30–34].

Additional Effects of Bronchoalveolar Lavage

A common, additional procedure of FB is bronchoalveolar lavage (BAL). It has been shown to be tolerated even in critically ill children [35, 36]. What are the additional physiological consequences of BAL? The potential for hypoxemia is

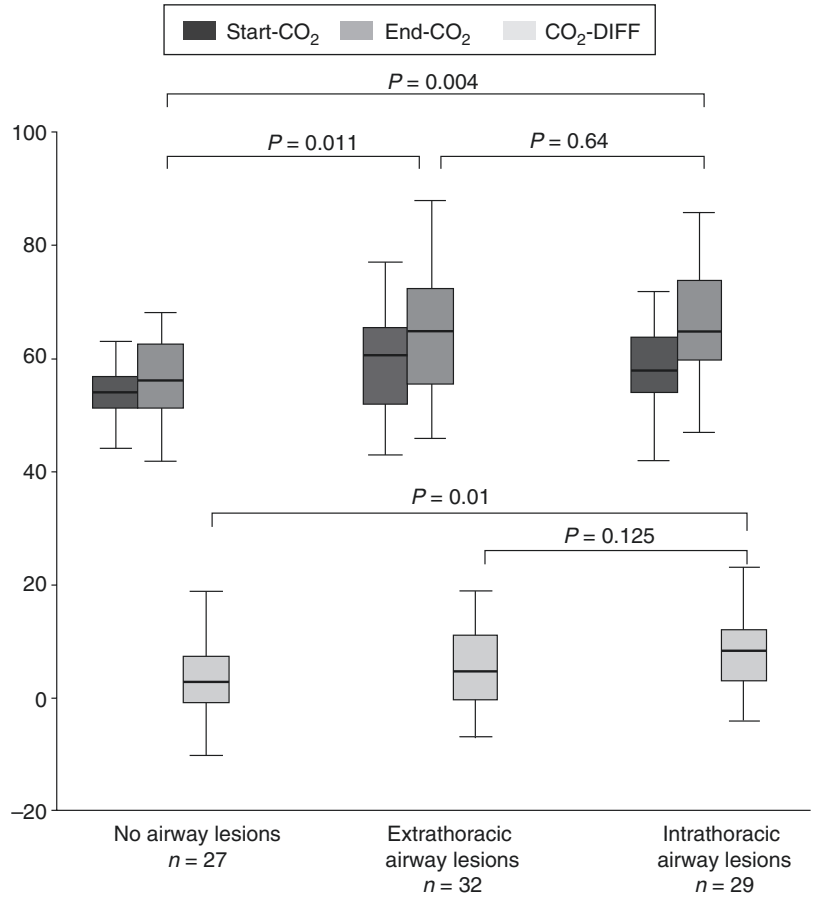

Fig. 12.8 Box-plot of median and interquartile range of endoscopic intratracheal CO_2 measurements on the initial pass of the bronchoscope (Start-CO_2), at the completion of the procedure (End-CO_2), and the CO_2-change (End-CO_2 minus Start-CO_2), in the children grouped by airway lesion type (no airway lesions, extrathoracic, and intrathoracic airway lesions). The *P*-values refer to comparison between the groups using Wilcoxon test for unpaired data and Mann-Whitney for paired comparisons (*P*-values in the results section for comparison of more than two groups refers to Kruskal-Wallis test). (Reprinted from Chang et al. [28], p. 653, with permission from John Wiley & Sons, Inc.)

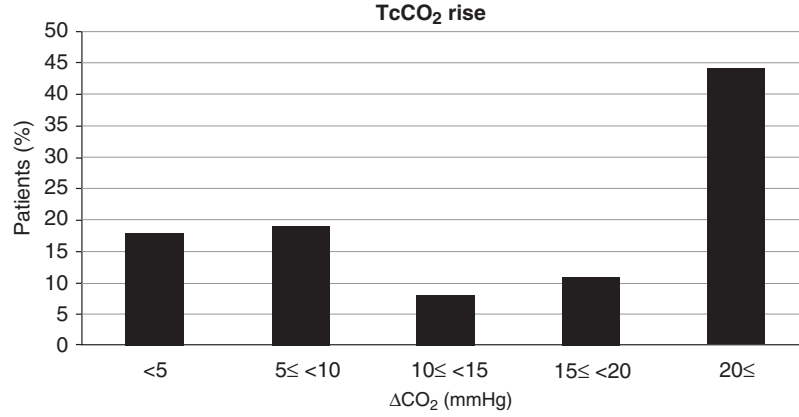

Fig. 12.9 Distribution of elevation of transcutaneous pCO2 in children undergoing flexible bronchoscopy. (Adapted from Sadot et al. [29], p. 1180, with permission from John Wiley & Sons, Inc.)

further increased with BAL [18, 23, 36, 37]. Another physiological finding associated with BAL is transient fever, especially in young patients [36, 38–40].

The physiological effects of large volume BAL with 1000 ml saline lobar lavage was studied in a comprehensive fashion in healthy adult patients by Burns et al. They found a mean decrease of 30 torr in PaO_2 (Fig. 12.10), with the greatest decrease occurring during insertion of the bronchoscope and during lobar bronchus occlusion with an inflation cuff.

Ventilation and perfusion scans revealed abnormalities of decreased ventilation and perfusion persisting for hours with return to normal usually by 24 hours. Ventilation defects were not altered by use of supplemental oxygen. However, perfusion defects were decreased in those who were treated with supplemental oxygen.

PaO_2 was significantly lower after lavage in subjects who had received supplemental oxygen during FB and discontinued at the end of FB, and recovered more slowly than subjects receiving no supplemental oxygen! Hypoxemia was noted to persist up to 8 hours in the group who had received supplemental oxygen (Fig. 12.11). It was concluded that the use of supplemental oxygen resulted in less matching of the ventilation-perfusion abnormalities induced by lavage, with consequent effects on gas exchange following the procedure.

Furthermore, temperature differences of the lavage have been evaluated and found to lead to dissimilar results. Room temperature, compared to body temperature, saline lavage resulted in a greater changes in lung function, performed within 2–4 hours after lavage, including declines in vital capacity (VC), total lung capacity (TLC) (20% decrease), and $FEF_{25–75}$, and an increase in residual volume. In contrast, subjects lavaged with body temperature saline did not show significant declines in VC, TLC, $FEF_{25–75}$, but did have increased residual volume. No significant changes were noted in PaO_2, FEV_1, or Raw in either group. The authors stated that the reasons for the lavage temperature effect were obscure [26].

Ettensohn et al. studied the lung function effects of repeated BAL with 120 ml aliquots (3–5 procedures/person with an average interval

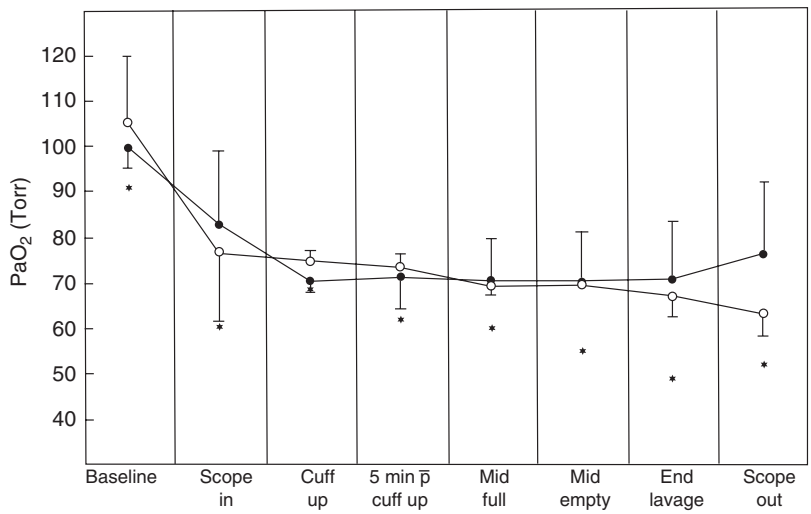

Fig. 12.10 Arterial PO_2 during lavage with saline at room temperature with subjects breathing room air (• = mean values for lavaged subjects; O = mean values for control subjects; * = lowest Pao2 recorded in the entire group at each time point). Middle full and middle empty measurements were made after the fifth aliquot, with that aliquot in the lung (full) or after it had been aspirated (empty). Brackets indicate one standard deviation of the measurements. (Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Burns et al. [26], p. 697)

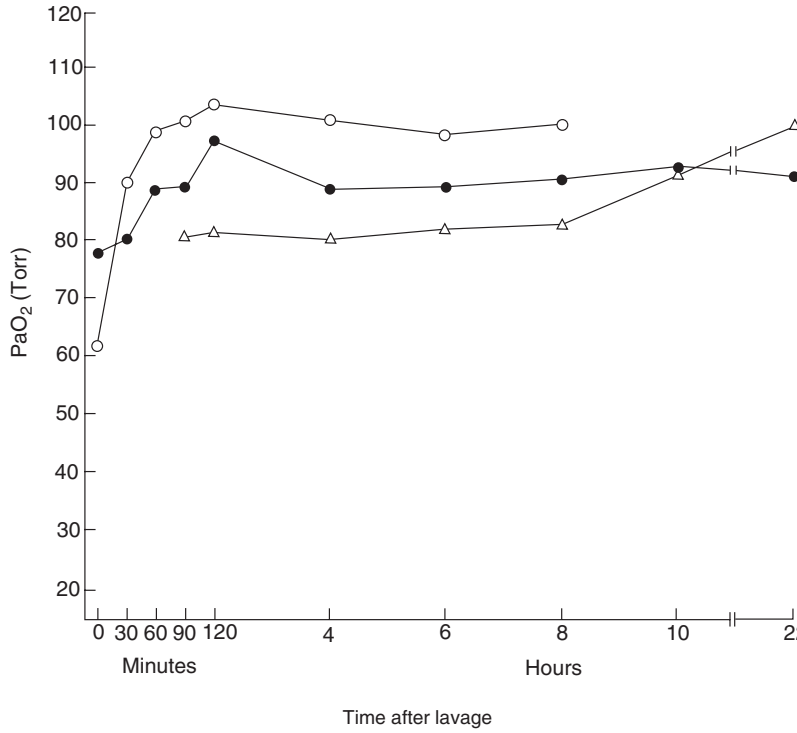

Fig. 12.11 Arterial PO_2 after lavage (• = mean values for subjects lavaged while breathing room air; A = mean values for subjects lavaged while receiving supplemental oxygen; O = mean values for control subjects). The control values at 30 and 60 min are mean values for the three room air control subjects breathing room air; thereafter, the values are the mean values for the combined group of room air and supplemental oxygen control subjects. (Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Burns et al. [26], p. 697)

of 4.7 months) in healthy adult volunteers. They found no persistent changes in pulmonary function tests, VC, TLC, FEV_1 or DLCO following repeated procedures [41].

In summary, BAL leads to additional physiological consequences, increasing with larger BAL volumes and room temperature more than body temperature lavage. While supplemental oxygen will moderate hypoxemia incurred during BAL, less matching of ventilation-perfusion abnormalities may lead to prolonged hypoxemia for hours after FB. Therefore, BAL should be performed with body temperature lavage and supplemental oxygen, with prolonged oxygen likely required after FB, especially with large volume BAL in sick patients.

Body Temperature Effects

Another physiological response to FB is fever. One prospective study evaluating fever within 24 hours after FB in children showed an overall incidence of 48% (44/91 patients). This study reported a significant difference of 18.2% incidence of fever in patients having FB without BAL compared to 52.2% in the BAL group. The risk of fever was increased in children less than 2 years of age, presence of positive bacterial colonies in BAL, and abnormal bronchoscopic findings [38].

A fever incidence of 37.8% (56/148 children) was noted in another prospective study of fever following FB with BAL in children. In this study, a multivariate analysis revealed only one risk factor for fever, children less than 2 years of age

[39]. In a retrospective analysis, a 17% incidence of fever (defined ≥39 °C) was found after FB with BAL in non-critically ill, immunocompetent children with underlying pulmonary disease. In this study, an abnormal BAL fluid cell differential was associated with fever [40].

Intracranial Pressure Effects

Due to prior reports of increased intracranial pressure (ICP) during FB in adults with severe brain injuries, Kerwin et al. carried out a prospective study on changes in ICP during FB. This study also evaluated possible pharmacological protection [42].

This study showed immediate changes with a substantial but transient increase in ICP along with concomitant increase in mean arterial pressure. Consequently, cerebral perfusion pressure (CPP) remained close to baseline. ICP increased from a mean baseline ICP of 12.6 mmHg to a mean peak ICP of 38.0 mm Hg (Fig. 12.12). The procedure time was 6 minutes, and the average time for return of ICP to baseline was 13.9 minutes. Subgroup analysis comparing patients with a baseline ICP ≤10 mmHg vs >10 mmHg showed comparable patterns of increases in mean ICP and MAP, close to baseline CPP, and time of return to baseline. No persistent changes in ICP and no evident neurological sequelae from FB were noted in the patients with brain injury following FB.

Based on prior studies, they used a sedation, analgesia, paralysis, and topical anesthesia protocol of vecuronium, morphine, midazolam and, in the subgroup of patients with ICP >10 mmHg, nebulized 4% lidocaine mmHg. However, they found that this protocol did not completely blunt the increase in ICP. The authors suggested that detecting rapid, high rises in ICP from routine suctioning might be useful in the "discretion" for doing a FB.

In another study of adult patients with severe head injury, similar findings of clinically insignificant increase of ICP, with a mean increase of

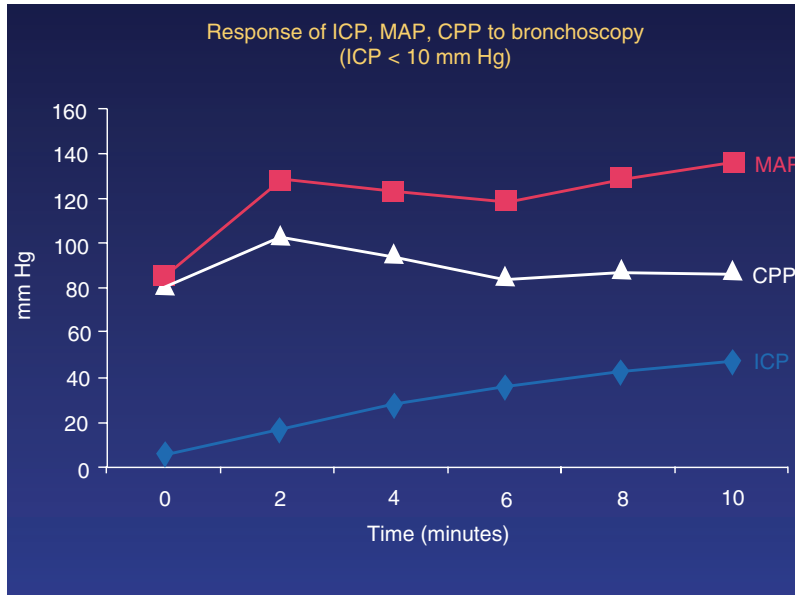

Fig. 12.12 Response of intracranial pressure (ICP), mean arterial pressure (MAP, and cerebral perfusion pressure (CPP) to flexible bronchoscopy in patients with baseline ICP ≤ 10 mm Hg. (Adapted from Kerwin et al. [42], p. 879. https://journals.lww.com/jtrauma/pages/articleviewer.aspx?year=2000&issue=05000&article=00011&type=abstract)

13.5 mm Hg in ICP and a mean increase in MAP of 19.2 mm Hg with consequent increase of CPP of 14% were noted, returning to baseline immediately following the procedure. No patients had changes in Glasgow Coma Scale or neurologic exam following FB [43].

Physiological Effects of Anesthetic Agents

While there is a specific consensus statement about sedation for FB in adults [44], no similar statement for pediatric FB sedation has been published. There are general pediatric guidelines about monitoring and management for sedation for diagnostic and therapeutic procedures by the American Academy of Pediatrics and American Academy of Pediatric Dentistry [45] and the Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018 [25]. Adequate sedation with airway management for pediatric FB is considered a requirement in order to improve patient comfort and anxiety, maintain hemodynamics, provide for adequate gas exchange, and provide conditions for a successful FB [15, 31].

A confounding variable in evaluating the data about the physiological effects of FB is variation in sedation and topical anesthesia, which are often not specified or quantified in studies in FB. There are studies in adult patients evaluating FB with only topical anesthesia and comparing groups receiving sedation vs no sedation. For example, using a verbal analog scale, Gonzalez et al. found that patients receiving sedation during FB had less cough, pain, sensation of asphyxiation, higher global tolerance, and lower heart rate and blood pressure responses compared to the no sedation patients [46]. Yung-Lun et al. also found that sedation resulted in similar patient subjective scores along with less hypertensive but more hypoxemic episodes that were transient and non-life-threatening [47].

Some of the anesthetic agents commonly used for pediatric FFB and their direct, physiological consequences will be reviewed. The reader is referred to the chapter by Bruins, Laverriere, and Kilbaugh in this book for further information on anesthesia for FB.

The most important adverse concern about sedation is respiratory depression. Minor, usually clinically insignificant consequences from anesthesia during FB may occur including transient hypoxemia and hypercapnia, transient apnea, cardiac arrhythmia (transient bradycardia and tachycardia), transient hypotension, as well as nausea and vomiting. However, significant anesthesia complications during FB can occur, including significant episodes of apnea, hypoxemia, hypercapnia, hypotension, nausea and vomiting, and aspiration [15, 16].

Lidocaine is the most commonly used topical anesthetic agent for FB. The primary concern is lidocaine toxicity. Lidocaine maximum dose is stated as 7–8 mg/kg for adults [44]. For children, 4.5 mg/kg for children has been recommended by Drugs.com [48], whereas an ERS Task Force on pediatric FB has indicated a maximum dose of 5–7 mg/kg for topical lidocaine [31]. In a study of lidocaine for pediatric FB, serum levels were monitored and doses up to 7 mg/kg (175 mg/m^2) and up to 7–8.5 mg/kg for longer procedures were considered safe for children [49]. Toxic doses lead to dose-dependent effects including hypotension, myocardial depression, seizures, unconsciousness, apnea, coma, and cardiovascular depression (Table 12.1) [50].

At topical anesthesia doses, lidocaine has been shown to have physiological effects of note for FB. It attenuates cardiovascular responses to

Table 12.1 Dose-dependent effects of lidocaine

Plasma lidocaine concentration (μg/ml)	Effect
1–5	Analgesia
5–10	Circumoral numbness Tinnitus Skeletal muscle twitching Systemic hypotension Myocardial depression
10–15	Seizures Unconsciousness
15–25	Apnea Coma
>25	Cardiovascular depression

Adapted from Table 10-2, Maheshwai and Naguib [50], p. 293

awake intubation [50]. There was one published report that topical lidocaine for FB in children exaggerated laryngomalacia [51]. However, this finding was refuted in a subsequent study [52].

Among the more common agents used during FB are benzodiazepines, opiates, and propofol [16, 44]. Midazolam is the most commonly used benzodiazepine for intravenous sedation in pediatrics. The most significant side effect of midazolam is dose-dependent decrease in ventilation by decreasing hypoxic drive. This effect is further exaggerated by additional use of opiates and other CNS-depressant drugs.

Midazolam also decreases upper airway activity and depresses the swallowing reflex. Hemodynamic effects include decreased systolic blood pressure and elevated heart rate. It causes dose-dependent changes in regional cerebral blood flow in brain regions associated with the normal functioning of arousal, attention, and memory. Midazolam results in little to no change in ICP in patients with decreased CNS compliance. Midazolam does not prevent cardiovascular responses to intubation [53].

Opiates (short-acting agents such as fentanyl and remifentanil are primarily used for FB) may have the physiological consequences of dose-dependent and gender-dependent depression of ventilation, bradycardia, with consequent decrease in blood pressure and cardiac output especially in neonates, and modest increases in ICP. As noted previously, opiate–benzodiazepine combinations may result in synergistic depression of ventilation [53, 54].

Propofol is a commonly used non-barbiturate, non-opiate, non-benzodiazapine IV sedation agent for FB. Potential physiological effects include decreased cerebral blood flow, intracranial pressure, systemic blood pressure, and dose-dependent respiratory depression. It can produce bronchodilation. Profound bradycardia and asystole have been reported in healthy adults [53]. With regard to upper airway physiology, vocal cord and pharyngeal function, with consequent increased risk for aspiration, are compromised during procedural sedation. A prospective study of propofol anesthesia in children showed return of normal vocal cord movement upon emergence from anesthesia, thus permitting adequate assessment of vocal cord function at the conclusion of FB [55].

Ketamine can result in bronchodilator activity, no significant respiratory depression, emergence delirium, and increased cerebral blood flow and metabolic rate with subsequent increased ICP, though this latter finding has not been universally noted in studies. Unique among injected anesthetics, ketamine does result in cardiovascular stimulation including increases in systemic and pulmonary artery blood pressure, heart rate, and cardiac output [53].

An additional sedative agent that causes only mild respiratory depression is the alpha-2 adrenergic agonist, dexmedetomidine. It may lead to bradycardia and hypotension. In addition, it results in prolonged recovery times compared to other sedative agents [53].

Thus, anesthesia for FB may result in significant physiological changes in addition to the changes from the manipulation of the bronchoscope. In the largest prospective study of complications of FB in children (1153 children), transient oxygen desaturation was significantly higher in those undergoing deep sedation (6.3%) vs conscious sedation (0.7%) [16].

Consequently, the bronchoscopy team should be vigilant about both the anesthesia and operation of the flexible bronchoscope for possible adverse events while monitoring the patient. Patients with significant underlying conditions including chronic cardiovascular disease, significant congenital airway disorders, severe obstructive sleep apnea, and other disorders predisposing to potential of significant airway obstruction are at further risk for greater physiological effects from FB with sedation [16, 25, 45]. Furthermore, greater potential for physiological changes should be anticipated to occur during interventional FB due to the increased complexity and procedure time [56].

Procedural Anxiety

In addition to the actual instrumentation and anesthesia for FB, other environmental factors may alter the physiological responses to procedures.

Preoperative anxiety is estimated to occur in up to 75% of children. As reviewed by Chow et al., preoperative anxiety can result in a number of negative postoperative outcomes including prolonged anesthesia induction, poorer postoperative recovery, and higher doses of postoperative analgesia [57]. Beyond increasing preoperative anesthesia, a number of non-pharmacologic measures have been utilized to reduce preoperative anxiety.

A Cochrane Collaboration analysis on non-pharmacological interventions to assist induction of anesthesia in children revealed that parental presence during induction of anesthesia does not diminish anxiety. Other measures such as parental acupuncture, clowns/clown doctors, playing videos of the child's choice during induction, low sensory stimulation, and hand-held video games were felt to be promising but not conclusively proven ways of reducing anxiety [58].

A recent systematic review suggested that audiovisual interventions are more effective than standard-of-care measures of non-intervention, parental presence, or low dose of sedative medication [57]. Preoperative music listening has also been shown to reduce preoperative anxiety in one study in children [59], with similar positive results on anxiety reduction in a study on music before FB in adults [60]. A meta-analysis in adults also found that music during FB lowered physiological responses of blood pressure and heart rate [61]. Reducing sensory stimuli and child life specialists are additional promising measures, which may reduce anxiety and possibly reduce sedation requirements for procedures [62]. Thus, non-pharmacological measures may be useful in reducing preoperative anxiety and, in the case of music, potentially reduce physiological responses during FB.

Clinical Implications of the Physiological Effects of Flexible Bronchoscopy

Flexible bronchoscopy has been safely performed in the sickest neonates and children in intensive care units, and children undergoing more complex interventions [15, 31, 35, 63, 64]. A comprehensive review of FB studies among critically ill children revealed that the most commonly reported adverse events were transient and included hypotension, hypoxemia, and/or bradycardia requiring minimal intervention [35].

The physiological changes induced by fiberoptic bronchoscopy have been reviewed. There should be caution in interpreting the published data on physiological effects of FB. Much of the available data presented were from studies in adult patients. Circumspection must be exercised in extrapolating these effects in children. Presumably, these effects in children would be greater due to higher airway resistance and smaller airways along with the relative size of the bronchoscope to the airways, especially in infants. In addition, other precautions in evaluating the studies include the presence of different underlying health conditions that can affect the degree of physiological effects, the variable techniques of FB used such as trans-nasal vs use of face mask, LMA, or through an endotracheal tube, the variable strategies of anesthesia used, and the lack of information about other factors such as procedure time, the relative size of the bronchoscope(s) used in relation to patient size, amount of suctioning, and experience of the individuals performing the procedures.

Nonetheless, the available information does provide important lessons in understanding the pathophysiology of many of the potential complications and the basis for monitoring in FB. We have also learned that there are potentially multiple controllable factors that can reduce adverse consequences of FB. These include the relative size of the bronchoscope being used in relation to the size of the patient's airways, the length of the procedure, suctioning, and anesthesia.

Thus, the physiological consequences of fiberoptic bronchoscopy point to the following procedural caveats (Table 12.2):

Twelve caveats for flexible bronchoscopy

1. Use the smallest bronchoscope necessary to accomplish the procedure in order to reduce airway obstruction effects.
2. Adequate topical anesthesia should be administered to avoid potential barotrauma

Table 12.2 Twelve caveats for flexible bronchoscopy (See text for details)

1. Use the smallest bronchoscope necessary to accomplish the procedure
2. Use and monitor topical anesthesia and sedation carefully
3. Administer supplemental oxygen and monitor oxygenation
4. Monitor for airway obstruction
5. Monitor ventilation
6. Keep suctioning to a minimum
7. Keep the procedure time to a minimum
8. Avoid "bronchoscopist's hypnosis"
9. For patients undergoing bronchoalveolar lavage (BAL), a) oxygen may be needed for hours after the procedure; b) use body temperature rather than room temperature lavage fluid especially for large volume BAL
10. In ventilated patients, monitor and adjust for hypoventilation and inadvertent auto-PEEP
11. In patients with airway hyperreactivity, consider bronchodilator prior to procedure
12. Carefully consider performing flexible bronchoscopy in children with high-risk conditions

from coughing, as well as to avoid potential cough-receptor-induced bronchospasm or laryngospasm. In addition, proceeding with flexible bronchoscopy should be delayed to allow for sufficient topical anesthesia and attenuation of cardiovascular response from topical anesthesia. Appropriate level of sedation should be provided and closely monitored.

3. Provide supplemental oxygen to prevent hypoxic events and monitor oxygen saturation closely. Oxygen saturation will tend to be stable even in the face of significant hypoventilation when supplemental oxygen is provided to the patient.
4. Monitor for airway obstruction from flexible bronchoscopy by observation of chest excursions and auscultation of breath sounds, especially in neonates and premature infants in whom significant airway occlusion may occur with introduction of the bronchoscope.
5. Continual monitoring of ventilatory function, such as capnography, is advised to supplement standard monitoring by observation and pulse oximetry.
6. Keep suctioning to a minimum to minimize the potential of reduced FRC and compromised gas exchange.
7. Keep the procedure time to a minimum in order to minimize physiological effects from instrumentation and prolonged sedation.
8. Avoid "bronchoscopist's hypnosis," that is, avoid being spellbound on the airway finding(s) and losing awareness of procedure time, the patient's physiological status, and the communication and teamwork during FB.
9. For patients undergoing bronchoalveolar lavage, especially large volume BAL, supplemental oxygen may be necessary for hours after the procedure. In addition, in order to reduce adverse lung function changes, the BAL solution should be warmed to body temperature.
10. To avoid hypoventilation and barotrauma from excessive, inadvertent auto-PEEP while performing FB during mechanical ventilation, ventilator settings may need to be adjusted. This may include modifying or discontinuing PEEP during ventilation, especially in volume control mode. Another strategy to minimize inadvertent auto-PEEP would be to consider, if feasible, changing to a larger endotracheal tube for the procedure.
11. Bronchodilator administration prior to the procedure should be considered in patients at risk for further adverse effects due to increased airway hyperreactivity.
12. Carefully consider the indication(s) and safety of FB in children with significant underlying health problems who might be especially impacted by even small and transient or potentially more significant physiological effects of FB. Consequently, those with greatest concern would include infants and very small or young children, patients with significant health conditions such as severe pulmonary or cardiac disease, severe pulmonary hypertension, premature infants with necrotizing enterocolitis and other children with compromised mesenteric blood flow, unstable or severe intracranial hypertension, or patients with a complex febrile seizure disorder [65].

We look for medicine to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing. The gap between what we know and what we aim for persists. And this gap complicates everything we do. —Atul Gawande, *Complications: A Surgeon's Notes on an Imperfect Science*

References

1. Lin CC, Wu JL, Huang WC. Pulmonary function in normal subjects after bronchoalveolar lavage. Chest. 1988;93:1049–53.
2. Salisbury BG, et al. Effects of fibreoptic bronchoscopy in respiratory performance in patients with chronic airways obstruction. Thorax. 1975;30:441–6.
3. Bellinger C, Bleecker ER, Peters S, Pascual R, Krings J, Smith R, Hastie AT, Moore WC. Effects of bronchoscopy on lung function in asthmatics. J Asthma. 2017;54:866–71. https://doi.org/10.1080/02770903.2016.1276587. Epub 2017 Jan.
4. Busse WW, Wanner A, Adams K, Reynolds HY, Castro M, Chowdhury B, Kraft M, Levine RJ, Peters SP, Sullivan EJ. Investigative bronchoprovocation and bronchoscopy in airway diseases. Am J Respir Crit Care Med. 2005;172:807–16. Epub 2005 July 14.
5. Moore WC, Evans MD, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, Erzurum SC, Curran-Everett D, Dweik RA, Gaston B, Hew M, Israel E, Mayse ML, Pascual RM, Peters SP, Silveira L, Wenzel SE, Jarjour NN. National Heart, Lung, and Blood Institute's Severe Asthma Research Group. Safety of investigative bronchoscopy in the Severe Asthma Research Program. J Allergy Clin Immunol. 2011;128:328–36.
6. Matsushima Y, Jones RL, King EG, Moysa G, Alton JDM. Alterations in pulmonary mechanics and gas exchange during routine fiberoptic bronchoscopy. Chest. 1984;86:184–8.
7. Nakstad ER, Opdahl H, Skjønsberg OH, Borchsenius F. Intrabronchial airway pressures in intubated patients during bronchoscopy under volume controlled and pressure controlled ventilation. Anaesth Intensive Care. 2011;39:431–9.
8. Lindholm CE, Ollman B, Snyder JV, Millen EG, Grenvik A. Cardiorespiratory effects of flexible fiberoptic bronchoscopy in critically ill patients. Chest. 1978;74:362–8.
9. Lawson RW, Peters JI, Shelledy DC. Effects of fiberoptic bronchoscopy during mechanical ventilation in a lung model. Chest. 2000;118:824–31.
10. Lindgren S, Odenstedt H, Erlandsson K, Grivans C, Lundin S, Stenqvist O. Bronchoscopic suctioning may cause lung collapse: a lung model and clinical evaluation. Acta Anaesthesiol Scand. 2008;52(2):209–18. Epub 2007 Nov 13.
11. Hannania S, Barak M, Katz Y. Unilateral negative-pressure pulmonary edema in an infant during bronchoscopy. Pediatrics. 2004;113:e501–3.
12. Ricou B, Grandin S, Nicod L, Thorens JB, Suter PM. Adult and paediatric size bronchoscopes for bronchoalveolar lavage in mechanically ventilated patients: yield and side effects. Thorax. 1995;50:290–3.
13. Trachsel D, Erb TO, Frei FJ, Hammer J, Swiss Paediatric Respiratory Research Group. Use of continuous positive airway pressure during flexible bronchoscopy in young children. Eur Respir J. 2005;26:773–7.
14. Hsia D, DiBlasi RM, Richardson P, Crotwell D, Debley J, Carter E. The effects of flexible bronchoscopy on mechanical ventilation in a pediatric lung model. Chest. 2009;135:33–40.
15. Faro A, Wood RE, Schechter MS, Leong AB, Wittkugel E, Abode K, Chmiel JF, Daines C, Davis S, Eber E, Huddleston C, Kilbaugh T, Kurland G, Midulla F, Molter D, Montgomery GS, Retsch-Bogart G, Rutter MJ, Visner G, Walczak SA, Ferkol TW, Michelson PH, American Thoracic Society Ad Hoc Committee on Flexible Airway Endoscopy in Children. Official American Thoracic Society technical standards: flexible airway endoscopy in children. Am J Respir Crit Care Med. 2015;191(9):1066–80.
16. de Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. Eur Respir J. 2002;20:1271–6.
17. Payne CB Jr, Goyal PC, Gupta SC. Effects of transoral and transnasal fiberoptic bronchoscopy on oxygenation and cardiac rhythm. Endoscopy. 1986;18:1–3.
18. Montravers P, Ganzit R, Flombret MC, Blanchet F, Desmonts JM. Cardiopulmonary effects of bronchoalveolar lavage in critically ill patients. Chest. 1993;104:1541–7.
19. Trouillet JL, Guiguet M, Gibert C, Fagon JY, Dreyfuss D, Blanchet F, Chastre J. Fiberoptic bronchoscopy in ventilated patients. Evaluation of cardiopulmonary risk under midazolam sedation. Chest. 1990;97:927–33.
20. Nayci A, Atis S, Duce MN, Bayindir S, Tamer L, Ozturk C. Bronchoscopy is associated with decreased mesenteric arterial flow. Crit Care Med. 2008;36:2517–22. https://doi.org/10.1097/CCM.0b013e318183f35b.
21. Roth AG, Wheeler M, Stevenson GW, Hall SC. Comparison of a rigid laryngoscope with the ultrathin fibreoptic laryngoscope for tracheal intubation in infants. Can J Anaesth. 1994;41:1069–73.
22. Chegondi M, Francis T, Lin WC, Naqvi S, Raszynski A, Totapally BR. Effects of closed endotracheal suctioning on systemic and cerebral oxygenation and hemodynamics in children. Pediatr Crit Care Med. 2018;19:e23–30. https://doi.org/10.1097/PCC.0000000000001377.

23. Albertini RE, Harrell JH, Kurihara N, Moser KM. Arterial hypoxemia induced by fiberoptic bronchoscopy. JAMA. 1974;230:1666–7.
24. Schnapf B. Oxygen desaturation during fiberoptic bronchoscopy in pediatric patients. Chest. 1991;99:591–4.
25. Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. Anesthesiology. 2018;128:437–79. https://doi.org/10.1097/ALN.0000000000002043.
26. Burns DM, Shure D, Francoz R, Kalafer M, Harrell J, Witztum K, Moser KM. The physiologic consequences of saline lobar lavage in healthy human adults. Am Rev Respir Dis. 1983;127:695–701.
27. Evans EN, Ganeshalingam K, Ebden P. Changes in oxygen saturation and transcutaneous carbon dioxide and oxygen levels in patients undergoing fibreoptic bronchoscopy. Respir Med. 1998;92:739–42.
28. Chang AB, Moloney GE, Harms PJ, Masters IB. Endoscopic intratracheal carbon dioxide measurements during pediatric flexible bronchoscopy. Paediatr Anaesth. 2004;14:650–5.
29. Sadot E, Gut G, Sivan Y. Alveolar ventilation in children during flexible bronchoscopy. Pediatr Pulmonol. 2016;51:1177–82. https://doi.org/10.1002/ppul.23427. Epub 2016 Apr 8.
30. Alon D, Pertzov B, Gershman E, Frishman M, Rahman NA, Rosengarten D, Kramer MR. The safety of laryngeal mask airway-assisted bronchoscopy versus standard nasal bronchoscopy. Respiration. 2017;93:279–84. https://doi.org/10.1159/000456551. Epub 2017 Feb 8.
31. Midulla F, de Blic J, Barbato A, Bush A, Eber E, Kotecha S, Haxby E, Moretti C, Pohunek P, Ratjen F, ERS Task Force. Flexible endoscopy of paediatric airways. Eur Respir J. 2003;22:698–708.
32. Erb T, Hammer J, Rutishauser M, Frei FJ. Fibreoptic bronchoscopy in sedated infants facilitated by an airway endoscopy mask. Paediatr Anaesth. 1999;9:47–52.
33. Chhajed PN, Glanville AR. Management of hypoxemia during flexible bronchoscopy. Clin Chest Med. 2003;24:511–6.
34. Puangsuvan N, Tobias JD. Use of a helium-oxygen mixture to facilitate ventilation during bronchoscopy through a laryngeal mask airway. J Intensive Care Med. 2010;25:168–71.
35. Field-Ridley A, Sethi V, Murthi S, Nandalike K, Li ST. Utility of flexible fiberoptic bronchoscopy for critically ill pediatric patients: a systematic review. World J Crit Care Med. 2015;4:77–88.
36. de Blic J, Midulla F, Barbato A, Clement A, Dab I, Eber E, Green C, Grigg J, Kotecha S, Kurland G, Pohunek P, Ratjen F, Rossi G. Bronchoalveolar lavage in children. ERS Task Force on bronchoalveolar lavage in children. European Respiratory Society. Eur Respir J. 2000;15:217–31.
37. Schellhase DE, Fawcett DD, Schutze GE, Lensing SY, Tryka AF. Clinical utility of flexible bronchoscopy and bronchoalveolar lavage in young children with recurrent wheezing. J Pediatr. 1998;132:312–8.
38. Picard E, Schwartz S, Goldberg S, Glick T, Villa Y, Kerem E. A prospective study of fever and bacteremia after flexible fiberoptic bronchoscopy in children. Chest. 2000;117:573–7.
39. Fonseca MT, Camargos PA, Abou Taam R, Le Bourgeois M, Scheinmann P, de Blic J. Incidence rate and factors related to post-bronchoalveolar lavage fever in children. Respiration. 2007;74:653–8.
40. Schellhase DE, Tamez JR, Menendez AA, Morris MG, Fowler GW, Lensing SY. High fever after bronchoscopy and bronchoalveolar lavage in noncritically ill immunocompetent children. Pediatr Pulmonol. 1999;28:139–44.
41. Ettensohn DB, Jankowski MJ, Redondo AA, Duncan PG. Bronchoalveolar lavage in the normal volunteer subject. 2. Safety and results of repeated BAL, and use in the assessment of intrasubject variability. Chest. 1988;94:281–5.
42. Kerwin AJ, Croce MA, Simmons SD, Maxwell RA, Malhotra AK, Fabian TC. Effects of fiberoptic bronchoscopy on intracranial pressure in patients with brain injury: a prospective study. J Trauma. 2000;48:878–83.
43. Peerless JR, Snow N, Likavec MJ, Pinchak AC, Malangoni MA. The effect of fiberoptic bronchoscopy on cerebral hemodynamics in patients with severe head injury. Chest. 1995;108:962–5.
44. Wahidi MM, Jain P, dantz M, Lee P, Mackensen B, Barbour SY, Lamb C, Silvestri GA. American College of Chest Physicians Consensus Statement on the Use of Topical Anesthesia, Analgesia, and Sedation During Flexible Bronchoscopy in Adult Patients. Chest. 2011;140:1342–50.
45. Coté CJ, Wilson S; American Academy of Pediatrics; American Academy of Pediatric Dentistry. Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures. Pediatrics. 2019;143(6):e20191000.
46. Gonzalez R, De-La-Rosa-Ramirez I, Maldonado-Hernandez A, Dominguez-Cherit G. Should patients undergoing a bronchoscopy be sedated? Acta Anaesthesiol Scand. 2003;47:411–5.
47. Ni YL, Lo YL, Lin TY, Fang YF, Kuo HP. Conscious sedation reduces patient discomfort and improves satisfaction in flexible bronchoscopy. Chang Gung Med J. 2010;33:443–52.
48. drugs.com. Lidocaine Topical Dosage Guide with Precautions-Drugs.com. https://www.drugs.com/dosage/lidocaine-topical.html#Usual_Pediatric_Dose_for_Anesthesia. Medically reviewed by Drugs.com. Last updated on Nov 2, 2018. Accessed 20 Sept 2019.

49. Amitai Y, Zylber-Katz E, Avital A, Zangen D, Noviski N. Serum lidocaine concentrations in children during bronchoscopy with topical anesthesia. Chest. 1990;98:1370–3.
50. Maheshwai K, Naguib MA. Local anesthetics. In: Flood P, Rathmell JP, Shafer S, eds. Stoelting's Pharmacology & Physiology in Anesthetic Practice. 5th ed. Philadelphia, PA: Wolters Klumer; 2015. p. 282–313.
51. Nielson DW, Ku PL, Egger M. Topical lidocaine exaggerates laryngomalacia during flexible bronchoscopy. Am J Respir Crit Care Med. 2000;161:147–51.
52. von Ungern-Sternberg BS, Trachsel D, Zhang G, Erb TO, Hammer J. Topical lidocaine does not exaggerate laryngomalacia in infants during flexible bronchoscopy under propofol anesthesia. J Bronchology Interv Pulmonol. 2016;23:215–9.
53. Rathmell JP, Rosow CE. Intravenous anesthetic sedatives and hypnotics. In: Flood P, Rathmell JP, Shafer S, eds. Stoelting's Pharmacology & Physiology in Anesthetic Practice. 5th ed. Philadelphia, PA: Wolters Klumer; 2015. p. 160–203.
54. Cummings III K, Naguib MA. Opioid Agonists and antagonists. In: Flood P, Rathmell JP, Shafer S, eds. Stoelting's Pharmacology & Physiology in Anesthetic Practice. 5th ed. Philadelphia, PA: Wolters Klumer; 2015. p. 217–56.
55. Schroeck H, Fecho K, Abode K, Bailey A. Vocal cord function and bispectral index in pediatric bronchoscopy patients emerging from propofol anesthesia. Pediatr Pulmonol. 2010;45:494–9. https://doi.org/10.1002/ppul.21207.
56. de Lima A, Kheir F, Majid A, Pawlowski J. Anesthesia for interventional pulmonology procedures: a review of advanced diagnostic and therapeutic bronchoscopy. Can J Anaesth. 2018;65:822–36.
57. Chow CH, Van Lieshout RJ, Schmidt LA, Dobson KG, Buckley N. Systematic review: audiovisual interventions for reducing preoperative anxiety in children undergoing elective surgery. J Pediatr Psychol. 2016;41(2):v182–203. https://doi.org/10.1093/jpepsy/jsv094. Epub 2015 Oct 17.
58. Manyande A, Cyna AM, Yip P, Chooi C, Middleton P. Non-pharmacological interventions for assisting the induction of anaesthesia in children. Cochrane Database Syst Rev. 2015;7:CD006447. https://doi.org/10.1002/14651858.CD006447.pub3.
59. Franzoi MA, Goulart CB, Lara EO, Martins G. Music listening for anxiety relief in children in the preoperative period: a randomized clinical trial. Rev Lat Am Enfermagem. 2016;24:e2841. https://doi.org/10.1590/1518-8345.1121.2841.
60. Jeppesen E, Pedersen CM, Larsen KR, Walsted ES, Rehl A, Ehrenreich J, Schnoor S, Backer V. Listening to music prior to bronchoscopy reduces anxiety - a randomised controlled trial. Eur Clin Respir J. 2019;17(6):1583517. https://doi.org/10.1080/20018525.2019.1583517. eCollection 2019
61. Tam WW, Lo KK, Hui DS. The effect of music during bronchoscopy: a meta-analysis. Heart Lung. 2016;45:86–94. https://doi.org/10.1016/j.hrtlng.2015.12.004. Epub 2016 Jan 4.
62. Mason KP, Seth N. Future of paediatric sedation: towards a unified goal of improving practice. Br J Anaesth. 2019;122(5):652–61. https://doi.org/10.1016/j.bja.2019.01.025. Epub 2019 Mar 2.
63. Eber E, Antón-Pacheco JL, de Blic J, Doull I, Faro A, Nenna R, Nicolai T, Pohunek P, Priftis KN, Serio P, Coleman C, Masefield S, Tonia T, Midulla F. ERS statement: interventional bronchoscopy in children. Eur Respir J. 2017;50(6):1700901. https://doi.org/10.1183/13993003.00901-2017. Print 2017 Dec.
64. Bouso JM, Yendur O, Hysinger E, Planet PJ, Haas A, Goldfarb S, Piccione J. Endobronchial ultrasound-guided biopsy is feasible, safe, and improves diagnostic yields in immunocompromised children. Am J Respir Crit Care Med. 2020;201:384–6. https://doi.org/10.1164/rccm.201907-1372LE.
65. Wagener JS. Fatality following fiberoptic bronchoscopy in a two-year-old child. Pediatr Pulmonol. 1987;3:197–9.

Non-Bronchoscopic Assessment of the Airways

13

Alister J. Bates, Nara S. Higano, and Jason C. Woods

Overview

Bronchoscopy is the current gold standard for assessing structure, function, anomalies, and secretions related to the central airways [1]. However, bronchoscopic evaluations have some important limitations, particularly in the pediatric population. They are invasive and are typically performed under sedation; both of these factors may alter the behavior of the airway from its natural condition. Furthermore, findings can differ between rigid and flexible endoscopes, and there is continued debate over inter-operator agreement in airway assessment, for example, in determining the presence or absence of tracheomalacia in neonates [2]. These limitations have led to the development of alternative central airway assessment techniques.

Current clinical non-bronchoscopic assessment of the central airways is usually performed through radiological evaluation. Several different imaging modalities are used, including radiography, computed tomography (CT), and magnetic resonance imaging (MRI). The first of these provides a projection of the airway, and the latter two can provide 3D image volumes of the airway and surrounding structures. However, these methodologies have limitations in that they may not represent the air-

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_13

way in natural breathing, due to the breathing maneuver performed while the image was acquired (i.e., breath holds), sedation, and intubation. Imaging also does not usually provide functional information about the airway. Emerging Techniques Section of this chapter describes novel imaging-based techniques to address these limitations and to provide functional airway information such as the patient's breathing effort via computational fluid dynamics simulations of respiratory airflow.

Current Clinical Medical Imaging

Radiography

Initial airway assessment can be performed with frontal and lateral views of the neck and chest on X-ray radiographs (Fig. 13.1). Radiography exposes patients to very low doses of ionizing radiation, and it is generally considered safe in pediatrics [3, 4]. Radiographs are generally used for detecting the presence of foreign bodies within the airway [5, 6] and can also detect some airway conditions, such as croup [7, 8]. In addition, radiography can be used in the diagnosis of laryngomalacia [6], hypertrophy of the adenoids, palatine and lingual tonsils, and the tongue (macroglossia), and airway stenoses. Lateral cephalometry can be performed based on cranial radiographs, but a comparison between these measurements and findings from drug-induced sleep endoscopy (DISE) found little correlation between the methods, with the exception of narrowings in the retroglossal airway [9]. While radiographs may act as a first-line imaging assessment of airway conditions, the information garnered is limited since the single image is a projection of the airway, with little ability to quantify abnormalities or assess dynamics.

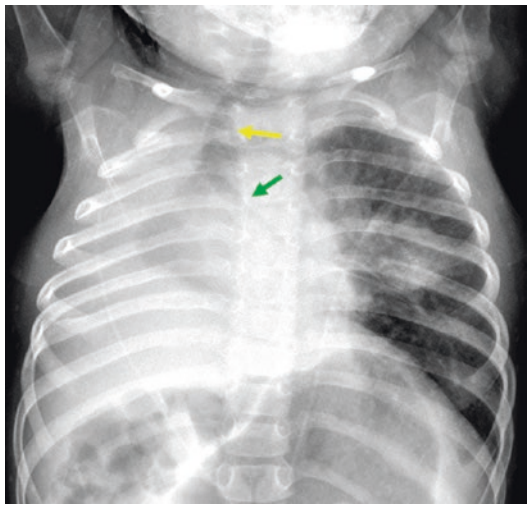

Fig. 13.1 X-ray radiograph**.** Chest X-ray radiograph in a 2-year-old female patient following a pneumonectomy for a congenital lung lesion. Abnormalities in the central airways are visible, including severe tracheal deviation (yellow arrow) and stenosis in the left main bronchus (green arrow). (Courtesy of Jason Woods, PhD, at Cincinnati Children's Hospital)

Computed Tomography

In current practice, X-ray computed tomography (CT) is considered the gold standard for noninvasive airway assessment [10–12]. Multi-detector CT (MDCT) provides detailed anatomic images with 2D multi-planar or 3D volume renderings. MDCT allows for shortened scan times, allowing for pediatric scans to be performed without the use of sedation or intubation, factors which have historically limited the use of CT for airway diagnostics; sedation can affect the muscle tone of structures surrounding the airways, and intubation can alter anatomical dynamics. The dynamics of the airway during typical breathing or coached inspiratory and expiratory breath-holds can be revealed by repeating MDCT to produce cine, 4D, or inspiratory-expiratory images (Fig. 13.2). However, the dynamic resolution can be limited by the speed of the gantry rotation, and repeated imaging increases the radiation exposure [10–12].

High spatial resolution is often necessary to detect abnormalities in the narrow nasal passages, such as turbinate hypertrophy, septal deviation, and pyriform aperture stenosis. The high-resolution of CT and its ability to produce high contrast between structures such as bone and soft tissue can be used to diagnose a large range of airway abnormalities and the underlying causes [13, 14].

The upper airways can be imaged via CT to determine the effect of surgical interventions to

correct conditions such as Pierre-Robin syndrome. Imaging can be performed preoperatively and postoperatively and the change in lumen size measured, information which may help the decision to decannulate patients [15]. In patients with obstructive sleep apnea (OSA), upper airway CT has been proposed to determine sites of obstruction, to assess surgical interventions, and also as a possible diagnostic alternative to polysomnography [16–18]. At present, while the importance of airway morphology in the severity of OSA is clear, no morphological parameter measured from CT images has been found to separate OSA patients from healthy individuals [19]. A comparison between CT measurements performed in awake patients and DISE classification of the upper airway in adult OSA patients revealed CT-matched DISE in identifying lateral collapse in the oropharynx [20].

In the trachea, CT can be used to diagnose subglottic stenosis and assess the severity of the stenosis [21]. Tracheomalacia (TM) can be analyzed via CT by comparing inspiratory and expiratory images of the airway (Fig. 13.2). The diagnosis of TM is made when the cross-sectional area of the trachea in the expiratory image is >50% less than on inspiration, a criterion originally developed in rigid bronchoscopy [22].

The advantages of CT over other imaging modalities are again the high contrast between the airway and surrounding structures, high spatial resolution, and the ability for 4D imaging. However, the major disadvantage of CT is the patient's exposure to ionizing radiation, and this concern particularly affects its use in pediatrics [23]. While the necessary dose of radiation has been greatly reduced [24, 25], CT is still rarely appropriate for serial imaging to assess changes in the airway as a child develops or to assess the efficacy of treatment strategies. While CT will remain a gold standard, emerging techniques in MRI have been demonstrated to provide images of the respiratory system that are comparable to the spatial and temporal resolution of CT (see Sect. Developments in Magnetic Resonance Imaging), but without breath-hold maneuvers, sedation/anesthesia, intubation, or ionizing radiation.

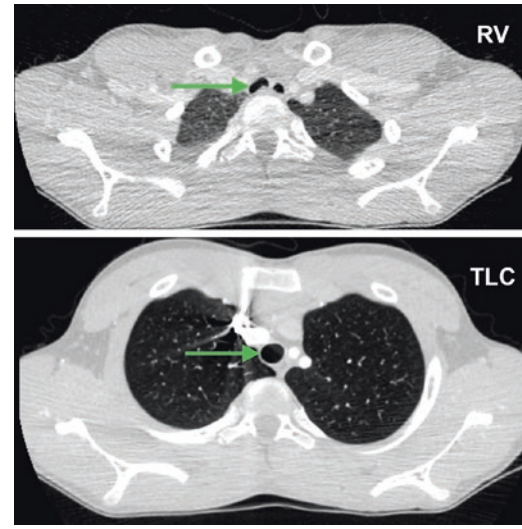

Fig. 13.2 CT of the dynamic trachea. Axial image slices from airway CT in a 14-year-old male with a highly dynamic chest wall. During a forced expiratory maneuver, at residual volume (RV), the trachea (green arrow) narrows significantly due to the narrowing of the chest. Comparison between the expiratory-phase (top) and inspiratory-phase (bottom – at total lung capacity, TLC) images demonstrates dynamic excessive collapse of the posterior tracheal wall. (Courtesy of Alister Bates, PhD, at Cincinnati Children's Hospital)

Magnetic Resonance Imaging

Magnetic resonance imaging provides high contrast between airway and the surrounding soft tissues without exposing the patient to any ionizing radiation. It is therefore suitable for evaluation of treatment through pre- and post-therapy imaging and for serial imaging of patients to monitor growth or disease progression, where multiple radiation exposures via CT would not be appropriate in the pediatric population.

Traditionally, an overall MRI exam consisting of multiple scans has taken 30–60 minutes to perform upper airway analysis [26]. While motion of non-compliant patients is a concern in pediatrics, new techniques such as compressed sensing have accelerated many sequences by up to four times [27]. These emerging techniques have obviated some of the disadvantages of a long acquisition time, through retrospective removal of data obscured by motion (see Sect. Developments in Magnetic Resonance Imaging) [28].

MRI has been also used clinically as a surgical planning tool for OSA. An MRI exam for OSA may include several scans designed to assess various aspects of a patient's anatomy. Proton density MRI provides a static high-resolution (sub millimeter in-plane resolution) structural image of the airway to highlight narrow points in the airway and the underlying anatomic cause (e.g., macroglossia) (Fig. 13.3) [29]. Cine MRI can provide real-time 2D slices of the airway at high temporal resolutions (e.g., ~3 images per second) to show the motion of the airway and any collapse during an individual breath [29]. Cine MRI is often repeated in several planes such as a midline sagittal plane to reveal anterior-posterior airway collapse, and axial planes at various locations in the airway to assess retropalatal and retroglossal collapse [30–32]. T_2-weighted turbo spin echo imaging can provide contrast in the soft-tissue structures surrounding the airway (e.g., distinguishing the tongue from the lingual tonsils) [29].

Ultrasound

Ultrasound is a fast imaging modality that is tolerated by the majority of pediatric patients, and like MRI, it is considered very safe, as it does not use ionizing radiation. The real-time nature of ultrasound makes it an ideal technique to determine correct positioning and appropriate sizing of an endotracheal tube [33].

Applications of airway ultrasound include assessment of soft-tissue masses in the neck [26] and guidance for percutaneous tracheostomy [34, 35]. There has been good agreement with endoscopic findings in evaluating vocal cord palsy in children up to 12 years old (81% agreement with endoscopy) [36], in identifying anatomy of subglottic hemangioma [37], and in identifying epiglottitis in patients over 15 years of age [38]. Additionally, ultrasound has been shown to give good agreement with MRI in terms of measuring the minimum airway diameter found in subglottic stenosis [39].

However, a major challenge of airway ultrasound is that air does not propagate the ultrasonic sound waves as effectively as tissues. Thus, it is particularly challenging to image structures surrounded by air, such as the epiglottis and soft palate [33, 40]. As a result, ultrasound has not been widely adopted for airway imaging.

Fluoroscopy

Fluoroscopy provides a continuous X-ray projection through the airway at high temporal resolution for ~10–20 seconds of breathing and has been used to assess motion of the airway in conditions such as OSA, laryngomalacia, or tracheomalacia [31]. A comparison of sleep fluoroscopy to direct laryngoscopy and bronchoscopy to identify upper airway obstruction in 50 pediatric patients found that sleep fluoroscopy identified sites of obstruction not recognized on direct laryngoscopy and bronchoscopy in 54% of cases

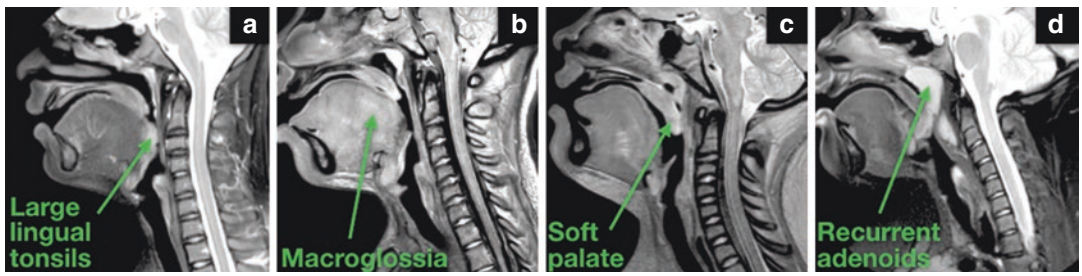

Fig. 13.3 MRI of obstructive sleep apnea. Sagittal static high-resolution MRI of patients with persistent obstructive sleep apnea (OSA) post-adenotonsillectomy. Each panel shows a patient with a specific cause of their OSA, which was identified by MRI. The condition was then treated with the following procedures: (**a**) lingual tonsillectomy, (**b**) partial midline glossectomy, (**c**) uvulopalatopharyngoplasty, and (**d**) revision adenoidectomy. (Courtesy of Alister Bates, PhD, at Cincinnati Children's Hospital)

and altered the course of treatment in 52% of cases [41].

In patients who have contraindications for MRI, such as those with hypoglossal nerve stimulators or metallic dental work (which is MR-safe but yields image artifacts), fluoroscopy can be used as an alternative for assessment of airway dynamics. MR-incompatible devices such as nerve stimulators are becoming increasingly popular treatment options for patients with OSA, and fluoroscopy can reveal in-plane airway dynamics post-treatment [42]. However, as fluoroscopy requires cumulative exposure to ionizing radiation, use of a fluoroscope cannot be justified solely by the sensitivity of the test [43], and use of airway fluoroscopy is decreasing in favor of other methods.

Virtual Bronchoscopy

Virtual bronchoscopy is a technique in which the airway structure is digitally recreated from high-resolution 3D images. In current clinical practice, these images are usually generated via CT, although emerging MRI techniques may provide a nonionizing alternative for this technique (see Sect. Developments in Magnetic Resonance Imaging below). On virtual bronchoscopy, a reader's viewpoint is placed within the airway, in the position where the endoscopic camera lens would be in bronchoscopy (Fig. 13.4). This viewpoint can then be moved along the airway, again as in bronchoscopy. Two techniques exist for displaying the airway: surface rendering and volume rendering. In surface rendering, the airway wall surface is digitally recreated where the image transitions from tissue to airway. When based on CT imaging, the transition can often be detected automatically due to the large change in Hounsfield intensity units between air and surrounding tissue. In volume rendering, each voxel in the image is represented in 3D space, with higher-intensity regions of the image (i.e., soft tissue) drawn opaquely and lower-intensity regions (i.e., air in the airway) drawn with more transparency. Therefore, the lumen is completely transparent, and placing the viewpoint inside the lumen reveals the first visible opaque region – the airway wall.

The primary function of virtual bronchoscopy is to present radiologic imaging in a format with which bronchoscopists are familiar. Virtual bronchoscopies can reveal the branching structure of the major airways, stenoses [5, 10], obstructions, and airway abnormalities such as tracheal diverticulum. However, each of these conditions is apparent directly from the radiological images [44–46], and the virtual bronchoscopy is not necessary for diagnosis. Due to virtual bronchoscopy's reliance on the initial imaging, it can only render the behavior of the airway during imaging: dynamic virtual bronchoscopy, comparison of the airway in inspiration and expiration, and breathing maneuvers such as induced coughing can only be performed if images of these behaviors were captured. Virtual bronchoscopy has been compared to flexible bronchoscopy in the diagnosis of pediatric tracheomalacia and was found to be specific, but not sensitive [47].

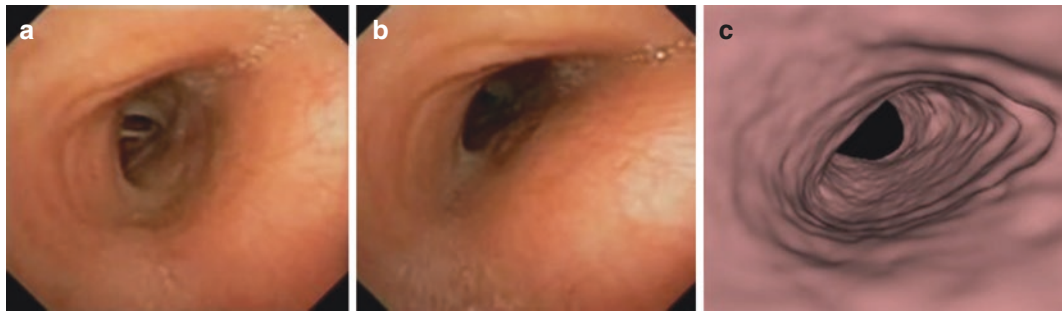

Fig. 13.4 Invasive and CT-based virtual bronchoscopy. Mild tracheomalacia in the middle and lower trachea of a pediatric patient are observed on both flexible bronchoscopy (**a** and **b**, respectively) and also on virtual bronchoscopy generated from high-resolution computed tomography (CT) images. (From: Su et al. [47])

Emerging Techniques

The ultimate goal of airway analysis is to detect the degree to which airway anatomy and motion affect each patient's ventilation and work of breathing, and how this relationship changes with airway abnormalities. For example, understanding how much a subglottic stenosis increases a patient's work of breathing can inform the clinical recommendation or rapidity of intervention. While current clinical imaging methods can provide useful information on airway abnormalities, they have limitations related to increased patient risks, nonrepresentative breathing conditions, lack of quantitative assessment, and lack of evaluation of airway function. Novel techniques for airway imaging are being developed that address many of the challenges of current clinical methods and may answer questions on airway function in a wide range of airway abnormalities.

Developments in Magnetic Resonance Imaging

Recent imaging developments in MRI have allowed similar capabilities to that of airway CT, without requiring nonionizing radiation. Radial ultrashort echo-time (UTE) MRI is a technique widely used for pulmonary imaging in the research setting. By sampling the rapidly decaying pulmonary MR signal much earlier than conventional MRI (on order of <100 μs, compared with ~0.5–3 ms depending on magnetic field strength) [48], UTE MRI can yield images with resolution (~0.7 mm isotropic) and proton-density image intensity approaching that of CT [49–51]. The time-course of specific UTE MRI raw data also allows the physiologic and bulk motion of the patient during imaging to be assessed retrospectively. Using this information, data acquired while the patient was noncompliantly moving can be discarded and an image created without motion artifact, assuming a reasonable period of quiescent breathing [28]. Furthermore, diaphragm motion can also be detected using similar UTE MRI raw data, allowing retrospective respiratory gating of images from a scan acquired during tidal breathing. Using this technique, high-resolution images show the patient's typical airway structure at several instants throughout the breathing cycle. UTE MRI has been used to quantitatively assess tracheomalacia in neonates with various

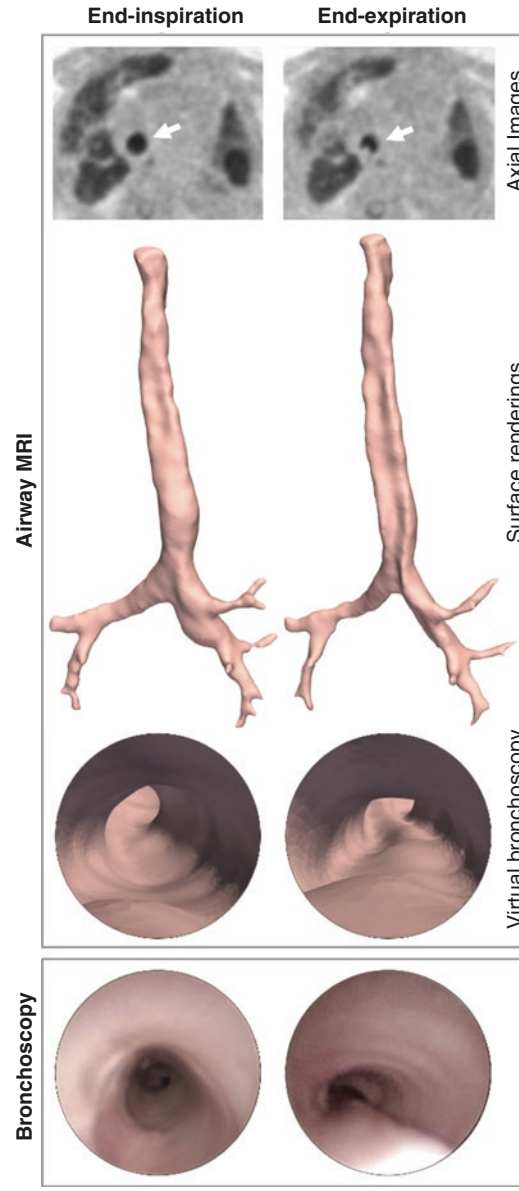

Fig. 13.5 MRI-based virtual bronchoscopy. Severe tracheomalacia in the middle and lower trachea of a male infant with bronchopulmonary dysplasia (BPD) can be observed in the axial slices (top row, arrows), surface renderings (second row), and virtual bronchoscopic views from high-resolution ultrashort echo-time (UTE) MRI, which does not require sedation or ionizing radiation. These MRI-based findings are comparable to those seen on invasive, sedated bronchoscopy (bottom row). (Courtesy of Jason Woods, PhD, Alister Bates, PhD, and Nara Higano, PhD, at Cincinnati Children's Hospital)

respiratory conditions (Fig. 13.5), obtaining good agreement with bronchoscopy [52], and for presurgical planning in patients with tracheoesophageal fistulas (Fig. 13.6) [53].

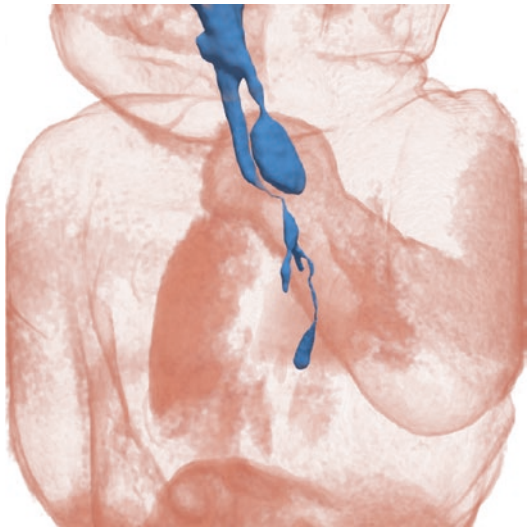

Fig. 13.6 3D anatomical rendering of neonatal congenital tracheoesophageal defects. Oblique left-posterior view of a 3D body volume rendering (red) and a surface rendering of the tracheal and esophageal anatomy (blue) in a female neonatal patient with esophageal atresia/tracheoesophageal fistula. Several anatomical abnormalities are evident: the large proximal esophageal pouch, long narrow fistula between the lower trachea and distal esophageal, and the severely compressed middle trachea. These 3D renderings are generated from high-resolution ultrashort echo-time (UTE) MRI, which does not require sedation or ionizing radiation and offer novel anatomical visualizations that can inform surgical planning decisions prior to operative treatment. (Courtesy of Jason Woods, PhD, Alister Bates, PhD, and Nara Higano, PhD, at Cincinnati Children's Hospital)

For some conditions, such as OSA, apneic events do not occur every breath, so it is necessary to obtain real-time cine images of the airway dynamics. Real-time cine MRI techniques have been developed to obtain MRI at high temporal resolution (~ten images per second), on a limited number of slices [54]. Other techniques have combined static high-spatial-resolution MRI with high-temporal resolution 4D MRI (~three 3D images per second; Fig. 13.7) to create virtual moving airway surfaces [55, 56].

Geometric Airway Measurements from Imaging

Traditional radiological quantification of airway anatomy has been limited to the measurement of a few key distances, such as the lumen diameter or cross-sectional area in a stenosis. While these values are of value, there is growing recognition that the size and shape of the entire airway influences the airflow within, rather than just a local constriction or in a single imaging slice [57]. Therefore, automatic techniques that measure many aspects of the airway's shape and size along the length of the airway have been developed.

To obtain accurate measurements of the size and the shape of the airway, the airway must be viewed perpendicularly to the lumen cross-section. This orientation can be difficult to

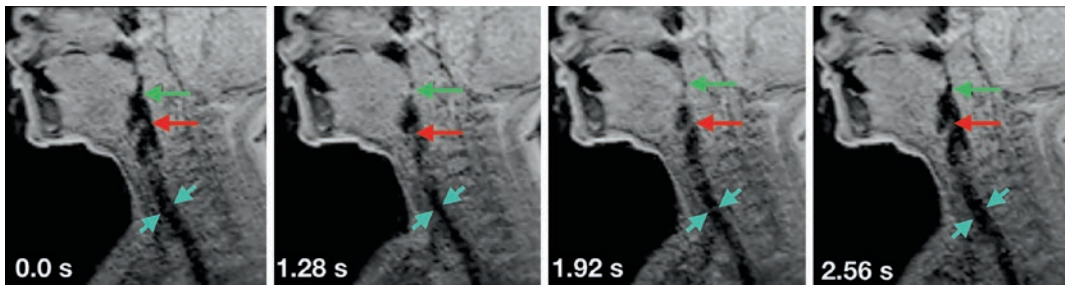

Fig. 13.7 3D cine MRI of obstructive sleep apnea. Midline sagittal slices through a 3D cine (or 4D) MRI image of an 11-year-old male patient with obstructive sleep apnea (OSA). A 3D image is captured every 0.32 s, and a panel is shown for four images throughout a breath. The motion of the airway as the patient breathes freely under sedation is indicated by the arrows. Red arrows indicate the motion of the epiglottis, green arrows show the different positions of the soft palate, and blue arrows show the changing patency of the trachea. (Courtesy of Alister Bates, PhD, at Cincinnati Children's Hospital)

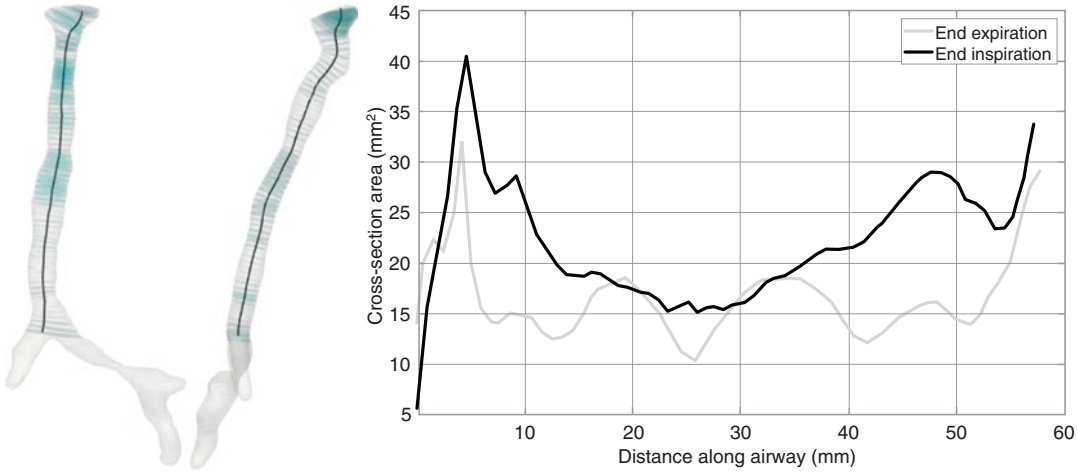

Fig. 13.8 Airway lumen measurements. Left: Coronal and sagittal views of an airway surface derived from a segmentation of ultrashort echo-time (UTE) MRI of a neonate with bronchopulmonary dysplasia. The airway surface is shown in gray, the airway centerline is shown in black, and disks representing the airway lumen 90° to the centerline are shown in blue at 1 mm intervals. Right: Measuring the cross-sectional area of these luminal disks along the length of the airway produces a map of airway area. Repeating these measurements during different phases of breathing demonstrates the dynamics of the airway through breathing (airway area at end-inspiration and end-expiration in black and gray, respectively). (Courtesy of Alister Bates, PhD, at Cincinnati Children's Hospital)

achieve by viewing imaging slices alone because the airway curves from the nasal and oral airways into the pharynx and the descending airway may not be aligned with the axes of the images. Images can be reformatted to create off-axes images, although this can be time consuming to perform along the entire airway, and the airway may not maintain the same axis along its entire length. An alternative approach involves creating a virtual airway surface via segmentation or edge detection of the airway wall from high-resolution images. A centerline can be produced following the path of the airway, as is often done in analysis of vasculature [58]. The airway can then be assessed relative to its centerline, instead of an arbitrary imaging plane, producing a true cross-sectional area, which is invariant to the position of the patient in the scanner and airway curvature (Fig. 13.8) [57, 59, 60].

Using these techniques, it has been demonstrated that airway curvature may play as significant a role as airway constriction in contributing to patient symptoms, despite current clinical guidelines only considering the latter [57, 59]. Repeating these measurements on the 4D imaging techniques used above allows analysis of how the airway size and shape change during a breath in dynamic conditions such as OSA and TM. For example, in neonatal TM, the ratio of the major and minor diameters has been found to be a strong indicator of tracheomalacia [52]. CT of patients with COPD revealed modest correlation between the area of the fourth and fifth tracheal branches and FEV_1 measurements [61].

Calculating Airway Function: Computational Fluid Dynamics

Both bronchoscopy and the imaging analysis techniques described in this chapter are visual or geometric assessments of the airway. These techniques reveal the size and shape of the airway but cannot reveal how these factors influence airflow. In cardiovascular medicine, several techniques have been developed to analyze blood flow through its velocity (measured via phase contrast MRI) and pressures (measured via cardiac catheterization). These imaging techniques cannot directly image the inhaled air since the flowing medium lacks sufficient density, but similar aerodynamic measures can be revealed by computa-

tional simulations of airflow known as computational fluid dynamics (CFD).

CFD can reveal the behavior of air as it is inhaled and exhaled via calculating the physics equation governing airflow (the Navier-Stokes equations). It can calculate the breathing effort used to move air in and out of the lungs, the pressures generated in moving the air, the forces that air pressure applies to the airway wall, and the transport of heat, water vapor, and inhaled toxic or therapeutic particles. This information can be used by clinicians to:

1. Determine the contribution of airway abnormalities to patient symptoms. For example, in a patient with both lung and airway complications (such as infants with bronchopulmonary dysplasia, BPD), CFD can reveal the extra effort needed to breathe due to just the airway abnormality [57].
2. Identify sites causing elevated airway resistance [62]. In OSA, it is common for patients to have multilevel obstruction. Using CFD, the local resistance at each of these locations can be mapped, and the cause of collapse at each location determined. This analysis can aid surgical planning by identifying the sites at which surgical interventions will cause the most benefit. This may not be apparent from imaging alone, as resistance in one region of the airway may cause collapse in an entirely different region.
3. Identify the causes of airway motion. For example, in OSA, some airway collapse is caused by low air pressure pulling the walls inwards (passive collapse), and other motion is caused by neuromuscular control [55, 56, 63, 64]. These two different types of motion may require different treatment strategies.
4. Particle inhalation can reveal deposition maps for inhaled therapeutic drugs; this can be used to determine the size and amount of particles necessary to obtain a certain dosage at a particular level of the airway [65–67].

An example of the clinical use of CFD was in the assessment of airway function in the first pediatric patient with a decellularized cadaveric transplanted trachea. The transplanted airway segment did not grow as rapidly as the host tracheal segments, leading to an hour-glass-shaped trachea. CFD revealed that the patient's breathing effort had doubled in the 4 years following the transplantation [62].

Although CFD offers the potential to provide clinically significant information, it requires accurate physiological and anatomic data in order to provide meaningful results. Historically, the computational power required for accurate simulations was prohibitive; so, many simulations were based on simplifications from real physiology and anatomy. For example, simple idealized airway geometries were used, steady flow rates were considered rather than reciprocating inhalation and exhalation, and airflow turbulence was greatly simplified or ignored. As computational power has increased, CFD simulations are now capable of closely replicating in vivo conditions. To perform accurate CFD, a virtual airway surface must be created that accurately follows the shape of the real airway. This is obtained by segmenting images of the airway, historically from CT, but new techniques for nonionizing, high-resolution 3D MRI can also now be used (such as UTE MRI; see above), providing the potential for serial studies of disease development and treatment efficacy. The accuracy of the airway segmentation can affect the results of the CFD simulation, with measures such as pressure drop, and airway resistance being particularly sensitive to changes in airway segmentation parameters. One study found that changing the CT image segmentation threshold from −800 to −300 Hounsfield Units changed the calculated unilateral nasal resistance by 52% [68]. The phase of breathing and breathing maneuver during which imaging is obtained must be considered, as the airway shape may be significantly different during a breath hold compared to vigorous inhalation and likewise between a breath-hold and free-breathing. Such differences in airway shape may significantly alter findings from the CFD simulation. The location and extent of the airway coverage must also be considered. Airflow is affected by the flow upstream and downstream of any point of interest; therefore, if nasal airflow is of interest, the exterior face (where flow devel-

ops) must be included in the virtual model [69], and if tracheal airflow is of interest, then the glottis must be included [70, 71]. In addition to an accurate virtual airway surface, accurate breathing flow-rate information must be provided to the model, and this can be obtained through a pneumotach worn by the patient during breathing, hot-wire anemometry, or by analyzing the change in lung volume [55, 56, 72, 73].

When considering airway conditions that involve significant motion, such as OSA or tracheomalacia, this motion should be incorporated into the CFD model (Fig. 13.9) [74]. Two techniques have been proposed: fluid structure interaction (FSI) and using prescribed wall motion obtained from dynamic imaging. FSI techniques model motion by calculating the deformation of the structures surrounding the airway based on their material properties, but to date, FSI simulations have incorporated only passive airway motion [74–79]. However, in OSA, synchronous imaging and breathing measurements have shown that there is a significant degree of neuromuscular control governing airway collapse in addition to passive motion [63, 64]. The second approach, which incorporates real airway wall motion from dynamic images via image registration and prescribing this motion to the virtual airway wall allows all forms of airway wall motion to be incorporated into the CFD simulation (Fig. 13.9) [55, 56].

Finally, airflow must be modeled appropriately. During restful breathing, airflow may be laminar in the nose, turbulent in the subglottic region, and transitional elsewhere in the central airways [65, 67, 80, 81]. Flow may be modelled as steady (not changing with time), quasi-steady (allowing the internal flow to change with time, but the airflow rate is constant) or fully unsteady (as in a realistic breath). While the most realistic

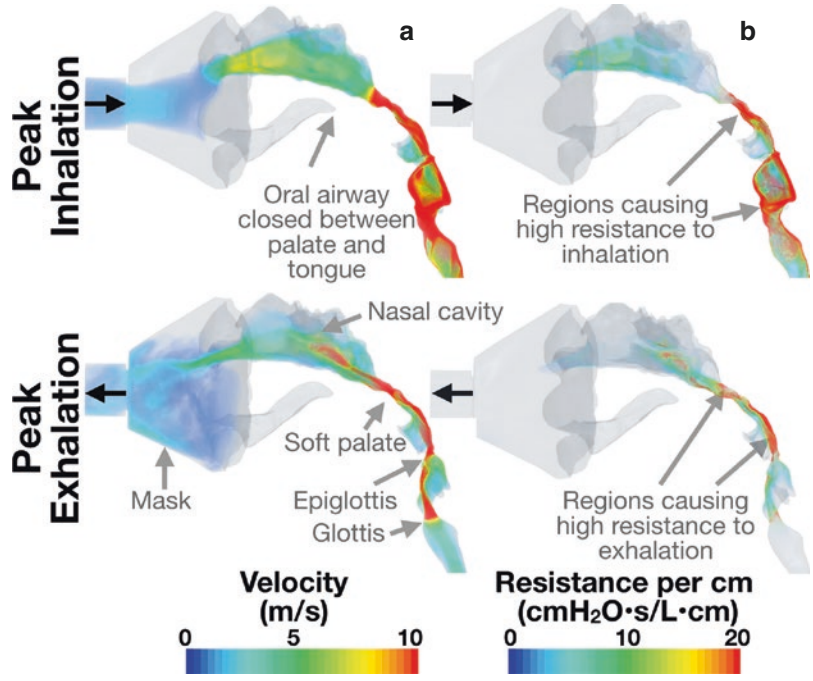

Fig. 13.9 CFD simulations. Computational fluid dynamics (CFD) simulation results in an 11-year-old patient with OSA. (**a**) Simulation results for airflow velocity at peak inhalation (upper) and peak exhalation (lower). The formation of high-speed jets can be seen in the oropharynx and after constrictions as the airflow navigates the epiglottis and glottis. (**b**) The resistance to airflow per centimeter of the airflow traversed. Regions of high resistance are highlighted in the retropalatal airway and hypopharynx. (Courtesy of Alister Bates, PhD, at Cincinnati Children's Hospital)

computational model would allow for fully turbulent, unsteady airflow, this may come at a high computational cost. As with the other simplifications and assumptions that can be made in CFD simulations, quicker approaches that provide the necessary clinical information may be adopted in preference to more realistic simulations that take much more time or computing power [80, 82].

Limitations of Image-Based Airway Assessment

All imaging techniques are sensitive to the position in which the patient is imaged and the phase of breathing during which images were obtained. Head position can change the interpretation of medical imaging and is sensitive to rotation and flexion in particular. A major disadvantage of imaging is that the position of the patient cannot be changed as easily as during bronchoscopy, where maneuvers such as jaw thrust may be performed to gain an impression of the airway in different positions. In pediatrics, maintaining the correct position for the duration of imaging may be particularly challenging, and immobilization devices or sedation may be necessary in children below 4 years of age [26].

The different modalities discussed in this chapter also use various techniques to control the phase of breathing in which imaging is obtained, but standard techniques do not capture the airway's behavior throughout natural breathing or through breathing maneuvers that may be induced during bronchoscopy, such as a cough.

Summary

Radiological evaluations of central airway abnormalities in pediatrics can provide novel information that is unique and beyond that acquired through bronchoscopic assessment. Current clinical practice frequently utilizes imaging modalities such as X-ray radiograph, CT, or MRI to noninvasively detect and assess static and dynamic airway conditions. Emerging techniques have obviated some of the challenges of current imaging methods related to patient safety and natural breathing conditions, particularly in MRI, and also can yield functional information related to abnormal airflow, such as with CFD simulations. These CFD simulations can quantify factors such as breathing effort, pressure losses, the forces acting on the airway walls, and inhaled particle depositions. With a high level of safety and repeatability, modern imaging methods allow for serial monitoring of disease progression and response to therapeutic and/or surgical treatment. Non-bronchoscopic tomographic imaging of the central airway has the potential to play a pivotal role in quantitatively assessing a wide range of pediatric airway conditions and in refining our understanding of how airway anatomy, motion, and airflow affect an individual patient's ventilation and work of breathing.

References

1. Hysinger E, Friedman N, Jensen E, Zhang H, Piccione J. Bronchoscopy in neonates with severe bronchopulmonary dysplasia in the NICU. J Perinatol [Internet]. Nature Publishing Group; 2019 [cited 2019 Feb 19];39(2):263–8. Available from: http://www.nature.com/articles/s41372-018-0280-y.
2. Burg G, Hysinger E, Hossain M, Wood R. Evaluation of agreement on presence and severity of tracheobronchomalacia in pediatric patients by dynamic flexible bronchoscopy. In: Proceedings of the American Thoracic Society.
3. Stagnaro N, Rizzo F, Torre M, Cittadini G, Magnano G. Multimodality imaging of pediatric airways disease: indication and technique. Radiol Med [Internet]. Springer Milan; 2017 [cited 2019 Feb 19];122(6):419–29. Available from: http://link.springer.com/10.1007/s11547-017-0737-7.
4. Koshy T, Misra S, Chatterjee N, Dharan BS. Accuracy of a chest X-Ray–based method for predicting the depth of insertion of endotracheal tubes in pediatric patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth [Internet]. W.B. Saunders; 2016 [cited 2019 Feb 19];30(4):947–53. Available from: https://www.sciencedirect.com/science/article/pii/S105307701600063X.
5. Lee EY, Restrepo R, Dillman JR, Ridge CA, Hammer MR, Boiselle PM. Imaging evaluation of pediatric trachea and bronchi: systematic review and updates. Semin Roentgenol. 2012;47(2):182–96.
6. Laya BF, Lee EY. Congenital causes of upper airway obstruction in pediatric patients: updated imaging techniques and review of imaging findings. Semin Roentgenol [Internet]. 2012 [cited 2019 Feb

19];47(2):147–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22370193.
7. Chapman T, Sandstrom CK, Parnell SE. Pediatric emergencies of the upper and lower airway. Appl Radiol. 2012;41:10–7.
8. Huang C-C, Shih S-L. Steeple sign of croup. N Engl J Med. 2012;367(1).
9. George JR, Chung S, Nielsen I, Goldberg AN, Miller A, Kezirian EJ. Comparison of drug-induced sleep endoscopy and lateral cephalometry in obstructive sleep apnea. Laryngoscope [Internet]. John Wiley & Sons, Ltd; 2012 [cited 2019 Feb 1];122(11):2600–5. Available from: http://doi.wiley.com/10.1002/lary.23561.
10. Lee EY, Greenberg SB, Boiselle PM. Multidetector computed tomography of pediatric large airway diseases: state-of-the-art. Radiol Clin North Am [Internet]. Elsevier; 2011 [cited 2019 Feb 8];49(5):869–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0033838911000765.
11. Lee EY. Advancing CT and MR imaging of the lungs and airways in children: imaging into practice. Pediatr Radiol [Internet]. Springer; 2008 [cited 2019 Feb 8];38(S2):208–12. Available from: http://link.springer.com/10.1007/s00247-008-0767-3.
12. Lee EY, Siegel MJ. MDCT of tracheobronchial narrowing in pediatric patients. J Thorac Imaging [Internet]. 2007 [cited 2019 Feb 8];22(3):300–9. Available from: https://insights.ovid.com/crossref?an=00005382-200708000-00020.
13. Sanal B, Demirhan N, Koplay M, Sadikoğlu MY, Gürpinar A. Congenital nasal pyriform aperture stenosis: clinical and radiologic findings and treatment. Jpn J Radiol. 2009;27(9):389–91.
14. Belden CJ, Mancuso AA, Schmalfuss IM. CT features of congenital nasal piriform aperture stenosis: initial experience. Radiology. 2013.
15. Rachmiel A, Emodi O, Aizenbud D. Management of obstructive sleep apnea in pediatric craniofacial anomalies. Ann Maxillofac Surg [Internet]. Wolters Kluwer – Medknow Publications; 2012 [cited 2019 Feb 1];2(2):111–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23483041.
16. Slaats MA, Van Hoorenbeeck K, Van Eyck A, Vos WG, De Backer JW, Boudewyns A, et al. Upper airway imaging in pediatric obstructive sleep apnea syndrome. Sleep Med Rev [Internet]. W.B. Saunders; 2015 [cited 2019 Feb 1];21:59–71. Available from: https://www.sciencedirect.com/science/article/pii/S1087079214000823.
17. Abramson Z, Susarla SM, Lawler M, Bouchard C, Troulis M, Kaban LB. Three-dimensional computed tomographic airway analysis of patients with obstructive sleep apnea treated by maxillomandibular advancement. J Oral Maxillofac Surg [Internet]. W.B. Saunders; 2011 [cited 2019 Feb 1];69(3):677–86. Available from: https://www.sciencedirect.com/science/article/pii/S0278239110016150.
18. Li H-Y, Lo Y-L, Wang C-J, Hsin L-J, Lin W-N, Fang T-J, et al. Dynamic drug-induced sleep computed tomography in adults with obstructive sleep apnea. Sci Rep [Internet]. Nature Publishing Group; 2016 [cited 2019 Feb 1];6(1):35849. Available from: http://www.nature.com/articles/srep35849.
19. Vos WG, De Backer WA, Verhulst SL. Correlation between the severity of sleep apnea and upper airway morphology in pediatric and adult patients. Curr Opin Allergy Clin Immunol [Internet]. 2010 [cited 2017 Feb 6];10(1):26–33. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00130832-201002000-00006.
20. Zhang P, Ye J, Pan C, Xian J, Sun N, Li J, et al. Comparison of drug-induced sleep endoscopy and upper airway computed tomography in obstructive sleep apnea patients. Eur Arch Oto-Rhino-Laryngology [Internet]. 2014 [cited 2019 Feb 1];271(10):2751–6. Available from: http://link.springer.com/10.1007/s00405-014-3051-1.
21. McDaniel LS, Poynot WJ, Gonthier KA, Dunham ME, Crosby and TW. Image-based 3-dimensional characterization of laryngotracheal stenosis in children. OTO Open [Internet]. SAGE Publications, Sage CA: Los Angeles, CA; 2018 [cited 2019 Feb 19];2(1):2473974X1775358. Available from: http://journals.sagepub.com/doi/10.1177/2473974X17753583.
22. Lee EY, Tracy DA, Bastos M d'Almeida, Casey AM, Zurakowski D, Boiselle PM. Expiratory volumetric MDCT evaluation of air trapping in pediatric patients with and without tracheomalacia. Am J Roentgenol [Internet]. American Roentgen Ray Society; 2010 [cited 2019 Feb 4];194(5):1210–5. Available from: http://www.ajronline.org/doi/10.2214/AJR.09.3259.
23. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: A retrospective cohort study. Lancet [Internet]. 2012 [cited 2018 Sep 14];380(9840):499–505. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22681860.
24. Singh S, Kalra MK, Moore MA, Shailam R, Liu B, Toth TL, et al. Dose reduction and compliance with pediatric CT protocols adapted to patient size, clinical indication, and number of prior studies. Radiology. 2009;252(1):200–8.
25. Yu H, Zhao S, Hoffman EA, Wang G. Ultra-low dose lung CT perfusion regularized by a previous scan. Acad Radiol. 2009;16(3):363–73.
26. Lee E. Pediatric radiology: practical imaging evaluation of infants and children. Lippincott Williams & Wilkins; 2017.
27. Lustig M, Donoho D, Pauly JM. Sparse MRI: the application of compressed sensing for rapid MR imaging. Magn Reson Med [Internet]. John Wiley & Sons, Ltd; 2007 [cited 2019 Feb 19];58(6):1182–95. Available from: http://doi.wiley.com/10.1002/mrm.21391.
28. Higano NS, Hahn AD, Tkach JA, Cao X, Walkup LL, Thomen RP, et al. Retrospective respiratory self-gating and removal of bulk motion in pulmonary

UTE MRI of neonates and adults. Magn Reson Med. 2017;77(3):1284–95.
29. Fleck RJ, Shott SR, Mahmoud M, Ishman SL, Amin RS, Donnelly LF. Magnetic resonance imaging of obstructive sleep apnea in children. Pediatr Radiol [Internet]. 2018 [cited 2018 Sep 14];48(9):1223–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30078047.
30. Nayak KS, Fleck RJ. Seeing Sleep: Dynamic imaging of upper airway collapse and collapsibility in children. IEEE Pulse [Internet]. 2014 [cited 2019 Feb 19];5(5):40–4. Available from: http://ieeexplore.ieee.org/document/6908108/.
31. Manickam PV, Shott SR, Boss EF, Cohen AP, Meinzen-Derr JK, Amin RS, et al. Systematic review of site of obstruction identification and non-CPAP treatment options for children with persistent pediatric obstructive sleep apnea. Laryngoscope [Internet]. Wiley-Blackwell; 2016 [cited 2018 Sep 13];126(2):491–500. Available from: http://doi.wiley.com/10.1002/lary.25459.
32. Shott SR, Donnelly LF. Cine magnetic resonance imaging: evaluation of persistent airway obstruction after tonsil and adenoidectomy in children with Down syndrome. Laryngoscope [Internet]. John Wiley & Sons, Inc.; 2004 [cited 2017 Mar 28];114(10):1724–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15454761.
33. Kundra P, Mishra SK, Ramesh A. Ultrasound of the airway. Indian J Anaesth. 2011;55(5):456.
34. Šustić A, Kovač D, Žgaljardić Z, Župan Ž, Krstulović B. Ultrasound-guided percutaneous dilatational tracheostomy: a safe method to avoid cranial misplacement of the tracheostomy tube. Intensive Care Med. 2000;26(9):1379–81.
35. Hatfield A, Bodenham A. Portable ultrasonic scanning of the anterior neck before percutaneous dilatational tracheostomy. Anaesthesia. 1999;54(7):660–3.
36. Vats A, Worley GA, de Bruyn R, Porter H, Albert DM, Bailey CM. Laryngeal ultrasound to assess vocal fold paralysis in children. J Laryngol Otol [Internet]. 2004 [cited 2019 Feb 27];118(06):429–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15285860.
37. Rossler L, Rothoeft T, Teig N, Koerner-Rettberg C, Deitmer T, Rieger CHL, et al. Ultrasound and colour Doppler in infantile subglottic haemangioma. Pediatr Radiol [Internet]. Springer-Verlag; 2011 [cited 2019 Feb 27];41(11):1421–8. Available from: http://link.springer.com/10.1007/s00247-011-2213-1.
38. Ko DR, Chung YE, Park I, Lee H-J, Park JW, You JS, et al. Use of bedside sonography for diagnosing acute epiglottitis in the emergency department. J Ultrasound Med [Internet]. John Wiley & Sons, Ltd; 2012 [cited 2019 Feb 27];31(1):19–22. Available from: http://doi.wiley.com/10.7863/jum.2012.31.1.19.
39. Lakhal K, Delplace X, Cottier JP, Tranquart F, Sauvagnac X, Mercier C, et al. The feasibility of ultrasound to assess subglottic diameter. Anesth Analg. 2007;104(3):611–4.
40. Singh M, Chin KJ, Chan VWS, Wong DT, Prasad GA, Yu E. Use of sonography for airway assessment: an observational study. J Ultrasound Med. 2010;29(1):79–85.
41. Gibson SE, Strife JL, Myer CM, O'Connor DM. Sleep fluoroscopy for localization of upper airway obstruction in children. Ann Otol Rhinol Laryngol [Internet]. SAGE Publications, Sage CA: Los Angeles, CA; 1996 [cited 2019 Feb 19];105(9):678–83. Available from: http://journals.sagepub.com/doi/10.1177/000348949610500902.
42. Goding GS, Tesfayesus W, Kezirian EJ. Hypoglossal nerve stimulation and airway changes under fluoroscopy. Otolaryngol Head Neck Surg. 2012;146(6):1017–22.
43. Isaiah A, Pereira KD. Laryngotracheal anomalies and airway fluoroscopy in infants. Int J Pediatr Otorhinolaryngol [Internet]. Elsevier; 2017 [cited 2019 Feb 19];97:109–12. Available from: https://www.sciencedirect.com/science/article/pii/S0165587617301337.
44. Teh BM, Hall C, Kleid S. Infected tracheocoele (acquired tracheal diverticulum): case report and literature review. J Laryngol Otol. 2011;125(5):540.
45. Sharma BG. Tracheal diverticulum: a report of 4 cases. Ear Nose Throat J. 2009;88(1):E11.
46. Soto-Hurtado EJ, Peñuela-Ruíz L, Rivera-Sánchez I, Torres-Jiménez J. Tracheal diverticulum: a review of the literature. Lung. 2006;184(6):303–7.
47. Su SC, Masters IB, Buntain H, Frawley K, Sarikwal A, Watson D, et al. A comparison of virtual bronchoscopy versus flexible bronchoscopy in the diagnosis of tracheobronchomalacia in children. Pediatr Pulmonol. 2017;52(4):480–6.
48. Hatabu H, Alsop DC, Listerud J, Bonnet M, Gefter WB. T2* and proton density measurement of normal human lung parenchyma using submillisecond echo time gradient echo magnetic resonance imaging. Eur J Radiol. 1999;29(3):245–52.
49. Johnson KM, Fain SB, Schiebler ML, Nagle S. Optimized 3D ultrashort echo time pulmonary MRI. Magn Reson Med. 2013;70(5):1241–50.
50. Lederlin M, Crémillieux Y. Three-dimensional assessment of lung tissue density using a clinical ultrashort echo time at 3 tesla: a feasibility study in healthy subjects. J Magn Reson Imaging. 2013;40(4):839–47.
51. Dournes G, Grodzki D, Macey J, Girodet P-O, Fayon M, Chateil J-F, et al. Quiet submillimeter MR imaging of the lung is feasible with a PETRA sequence at 1.5 T. Radiology. 2015;276(1):258–65.
52. Bates AJ, Higano NS, Hysinger EB, Fleck RJ, Hahn AD, Fain SB, et al. Quantitative assessment of regional dynamic airway collapse in neonates via retrospectively respiratory-gated ^{1}H ultrashort echo time MRI. J Magn Reson Imaging [Internet]. Wiley-Blackwell; 2018 [cited 2018 Sep 26]; Available from: http://doi.wiley.com/10.1002/jmri.26296.
53. Higano NS, Bates AJ, Tkach JA, Fleck RJ, Lim FY, Woods JC, et al. Pre- and post-operative visualization of neonatal esophageal atresia/tracheoesophageal fis-

tula via magnetic resonance imaging. J Pediatr Surg Case Rep [Internet]. 2018 [cited 2017 Oct 9];29:5–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29399473.
54. Wu Z, Chen W, Khoo MCK, Davidson Ward SL, Nayak KS. Evaluation of upper airway collapsibility using real-time MRI. J Magn Reson Imaging. 2016;44(1):158–67.
55. Bates AJ, Schuh A, Amine-Eddine G, McConnell K, Loew W, Fleck RJ, et al. Assessing the relationship between movement and airflow in the upper airway using computational fluid dynamics with motion determined from magnetic resonance imaging. Clin Biomech [Internet]. Elsevier; 2017 [cited 2017 Oct 24];0(0). Available from: http://linkinghub.elsevier.com/retrieve/pii/S0268003317302231.
56. Bates AJ, Schuh A, McConnell K, Williams BM, Lanier JM, Willmering MM, et al. A novel method to generate dynamic boundary conditions for airway CFD by mapping upper airway movement with non-rigid registration of dynamic and static MRI. Int j numer method biomed eng [Internet]. Wiley-Blackwell; 2018 [cited 2018 Sep 4];e3144. Available from: http://doi.wiley.com/10.1002/cnm.3144.
57. Bates AJ, Cetto R, Doorly DJ, Schroter RC, Tolley NS, Comerford A. The effects of curvature and constriction on airflow and energy loss in pathological tracheas. Respir Physiol Neurobiol. 2016;234:69–78.
58. Piccinelli M, Veneziani A, Steinman DA, Remuzzi A, Antiga L. A framework for geometric analysis of vascular structures: application to cerebral aneurysms. IEEE Trans Med Imaging IEEE. 2009;28(8):1141–55.
59. Bates AJ, Comerford A, Cetto R, Schroter RC, Tolley NS, Doorly DJ. Power loss mechanisms in pathological tracheas. J Biomech [Internet]. Elsevier; 2016 [cited 2016 May 13];49(11):2187–92. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0021929015006752.
60. Tschirren J, Hoffman EA, McLennan G, Sonka M. Intrathoracic airway trees: segmentation and airway morphology analysis from low-dose CT scans. IEEE Trans Med Imaging. 2005;24(12):1529–39.
61. Schroeder JD, McKenzie AS, Zach JA, Wilson CG, Curran-Everett D, Stinson DS, et al. Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. Am J Roentgenol [Internet]. American Roentgen Ray Society; 2013 [cited 2019 Feb 28];201(3):W460–70. Available from: http://www.ajronline.org/doi/10.2214/AJR.12.10102.
62. Hamilton NJ, Kanani M, Roebuck DJ, Hewitt RJ, Cetto R, Culme-Seymour EJ, et al. Tissue-engineered tracheal replacement in a child: a 4-year follow-up study. Am J Transplant [Internet]. Wiley Online Library; 2015;15(10):2750–7. Available from: http://doi.wiley.com/10.1111/ajt.13318.
63. Schwab RJ, Gefter WB, Hoffman EA, Gupta KB, Pack AI. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. Am Rev Respir Dis [Internet]. American Lung Association; 1993 [cited 2016 May 26];148(5):1385–400. Available from: http://www.atsjournals.org/doi/abs/10.1164/ajrccm/148.5.1385.
64. Schwab RJ, Gefter WB, Pack AI, Hoffman EA. Dynamic imaging of the upper airway during respiration in normal subjects. J Appl Physiol. 1993;74(4):1504–14.
65. Calmet H, Houzeaux G, Vázquez M, Eguzkitza B, Gambaruto AM, Bates AJ, et al. Flow features and micro-particle deposition in a human respiratory system during sniffing. J Aerosol Sci [Internet]. 2018 [cited 2018 May 29]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0021850218300375.
66. Calmet H, Kleinstreuer C, Houzeaux G, Kolanjiyil A V., Lehmkuhl O, Olivares E, et al. Subject-variability effects on micron particle deposition in human nasal cavities. J Aerosol Sci [Internet]. Pergamon; 2017 [cited 2017 Oct 24]; Available from: https://www.sciencedirect.com/science/article/pii/S0021850217301933.
67. Calmet H, Gambaruto AM, Bates AJ, Vázquez M, Houzeaux G, Doorly DJ. Large-scale CFD simulations of the transitional and turbulent regime for the large human airways during rapid inhalation. Comput Biol Med. 2016;69:166–80.
68. Cherobin GB, Voegels RL, Gebrim EMMS, Garcia GJM. Sensitivity of nasal airflow variables computed via computational fluid dynamics to the computed tomography segmentation threshold. 2018 [cited 2019 Jan 16]; Available from: https://doi.org/10.1371/journal.pone.0207178.t001.
69. Taylor DJ, Doorly DJ, Schroter RC. Inflow boundary profile prescription for numerical simulation of nasal airflow. J R Soc Interface [Internet]. 2010;7(44):515–27. Available from: http://rsif.royalsocietypublishing.org/cgi/doi/10.1098/rsif.2009.0306.
70. Lin CL, Tawhai MH, McLennan G, Hoffman EA. Characteristics of the turbulent laryngeal jet and its effect on airflow in the human intrathoracic airways. Respir Physiol Neurobiol Elsevier. 2007;157(2–3):295–309.
71. Collier GJ, Kim M, Chung Y, Wild JM. 3D phase contrast MRI in models of human airways: Validation of computational fluid dynamics simulations of steady inspiratory flow. J Magn Reson Imaging [Internet]. 2018 [cited 2018 Oct 16]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/29630757.
72. Rennie CE, Gouder KA, Taylor DJ, Tolley NS, Schroter RC, Doorly DJ. Nasal inspiratory flow: at rest and sniffing. Int Forum Allergy Rhinol. 2011;1(2):128–35.
73. Miyawaki S, Choi S, Hoffman EA, Lin CL. A 4DCT imaging-based breathing lung model with relative hysteresis. J Comput Phys [Internet]. Elsevier Inc.; 2016;326:76–90. Available from: https://doi.org/10.1016/j.jcp.2016.08.039.
74. Zhao M, Barber T, Cistulli PA, Sutherland K, Rosengarten G. Simulation of upper airway occlusion without and with mandibular advancement

in obstructive sleep apnea using fluid-structure interaction. J Biomech [Internet]. 2013 [cited 2016 May 26];46(15):2586–92. Available from: http://www.sciencedirect.com/science/article/pii/S0021929013003904.

75. Wang Y, Wang J, Liu Y, Yu S, Sun X, Li S, et al. Fluid-structure interaction modeling of upper airways before and after nasal surgery for obstructive sleep apnea. Int j numer method biomed eng [Internet]. John Wiley & Sons, Ltd; 2012 [cited 2017 Mar 3];28(5):528–46. Available from: http://doi.wiley.com/10.1002/cnm.1486.
76. Zhu JH, Lee HP, Lim KM, Lee SJ, Teo LSL, Wang DY. Passive movement of human soft palate during respiration: A simulation of 3D fluid/structure interaction. J Biomech [Internet]. 2012 [cited 2017 Mar 3];45(11):1992–2000. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0021929012002734.
77. Pirnar J, Dolenc-Grošelj L, Fajdiga I, Žun I. Computational fluid-structure interaction simulation of airflow in the human upper airway. J Biomech [Internet]. 2015 [cited 2017 Mar 3];48(13):3685–91. Available from: http://linkinghub.elsevier.com/retrieve/pii/S002192901500456X.
78. Ashaat S, Al-Jumaily AM. Reducing upper airway collapse at lower continuous positive airway titration pressure. J Biomech [Internet]. 2016 [cited 2017 Mar 3];49(16):3915–22. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0021929016311630.
79. Zhao M, Barber T, Cistulli P, Sutherland K, Rosengarten G. Predicting the treatment response of oral appliances for obstructive sleep apnea using computational fluid dynamics and fluid-structure interaction simulations. In: Volume 3A: Biomedical and biotechnology engineering [Internet]. 2013. p. V03AT03A051. Available from: http://proceedings.asmedigitalcollection.asme.org/proceeding.aspx?doi=10.1115/IMECE2013-62904.
80. Bates AJ, Doorly DJ, Cetto R, Calmet H, Gambaruto AM, Tolley NS, et al. Dynamics of airflow in a short inhalation. J R Soc Interface [Internet]. 2014 [cited 2015 Aug 12];12(102):20140880. Available from: http://rsif.royalsocietypublishing.org/cgi/doi/10.1098/rsif.2014.0880.
81. Zhao K, Dalton P, Yang GC, Scherer PW, Chemical M, Hall H, et al. Numerical modeling of turbulent and laminar air ow and odorant transport during Sniffing in the human and rat nose. Chem Senses. 2006;31(2):107–18.
82. Bates AJ, Comerford A, Cetto R, Doorly DJ, Schroter RC, Tolley NS. Computational fluid dynamics benchmark dataset of airflow in tracheas. Data Br [Internet]. Elsevier; 2017 [cited 2017 Feb 24];10:101–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27981200.

Flexible Bronchoscopy Training

14

Anastassios C. Koumbourlis

Introduction

Flexible bronchoscopy (FB) was introduced in the late 1960s, and it quickly became an integral part of the practice of pulmonary medicine in adults and children alike [1–3]. FB is a manual procedure and its success depends largely on the skills of the person who performs it. Although natural talent certainly helps, the ability to acquire (and perform) the skill depends in part on the way it is taught and on continuous practice.

Teaching is the transfer of knowledge, experience, and/or skill from one person to another; the way this transfer takes place constitutes the method of teaching. Historically, medicine (including the various procedures) was learnt through an apprenticeship. The apprentice would follow and observe the "Master," and it was the apprentice's responsibility to understand and not of the master to explain. The master would also decide for how long the apprenticeship would last and when the apprentice would be allowed to practice on his/her own.

The foundations of the modern teaching of procedures are attributed to William Stewart Halsted (the first Chief of Surgery at Johns Hopkins Hospital) who established the first formal surgical training. His approach was summarized in the concept of "See one, Do one, Teach one." The trainees were to observe a senior staff member doing a given procedure. The expectation was that after observing, the trainees would be able to perform the procedure on their own. Furthermore, they were expected to be able to teach others who had never done or observed one. Many of the pediatric bronchoscopists learnt according to this model. The trainees would initially observe an attending perform the bronchoscopy. They would then be allowed to hold the scope and navigate the easy parts of the airway (e.g., withdrawing the scope from the trachea), then the more challenging smaller airways until eventually they were allowed to perform the procedure on his/her own. During recent years, this model of learning has come into question and newer approaches have been proposed based on methods that are currently considered as more appropriate for adult learning [4–9].

As the procedure gained popularity and acceptance, the professional organizations such as American Thoracic Society (ATS), European Respiratory Society (ERS), and American College of Chest Physicians (ACCP) developed guidelines for its performance. Most of them focused on adult bronchoscopy (only two training guidelines have been specific to pediatrics). All the available documents have been largely limited to technical details on how the procedure should be performed but not on how it should be

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*,
Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_14

taught. Even less developed is the evaluation of the knowledge and skill of a bronchoscopist. There are no uniform criteria and methods to evaluate competency. The following chapter is focusing on the teaching of and training in flexible bronchoscopy of the pediatric pulmonary fellows. It reviews the literature as well as the author's personal and institutional experience. The chapter addresses three key questions: (1) What to teach, (2) how to teach it, and (3) how to assess the competency of the trainee.

Part 1. What to Teach?

The teaching of bronchoscopy consists of several elements (Fig. 14.1). The central one is of course to teach how to perform the actual procedure, that is, how to hold the bronchoscope and use its controls to navigate through the airways, as well as how to perform other procedures with it (e.g., bronchoalveolar lavage (BAL)) or through it (e.g., transbronchial biopsy (TBB) with the use of specific forceps). However, there are many equally important, although not as obvious, aspects that the bronchoscopist should master, including the following: (a) determining the indications for the procedure, (b) obtaining consent, (c) preparation of the patient and of the equipment for the procedure; (d) the care of the patient after the procedure, (e) the processing of the specimens that are obtained during the procedure, (f) the reprocessing of the equipment used in the procedure, and (g) the reporting of the findings of the procedure. Many of these elements are being discussed in detail in other chapters of this book and therefore in this chapter we focus primarily on the procedure, and how it can be

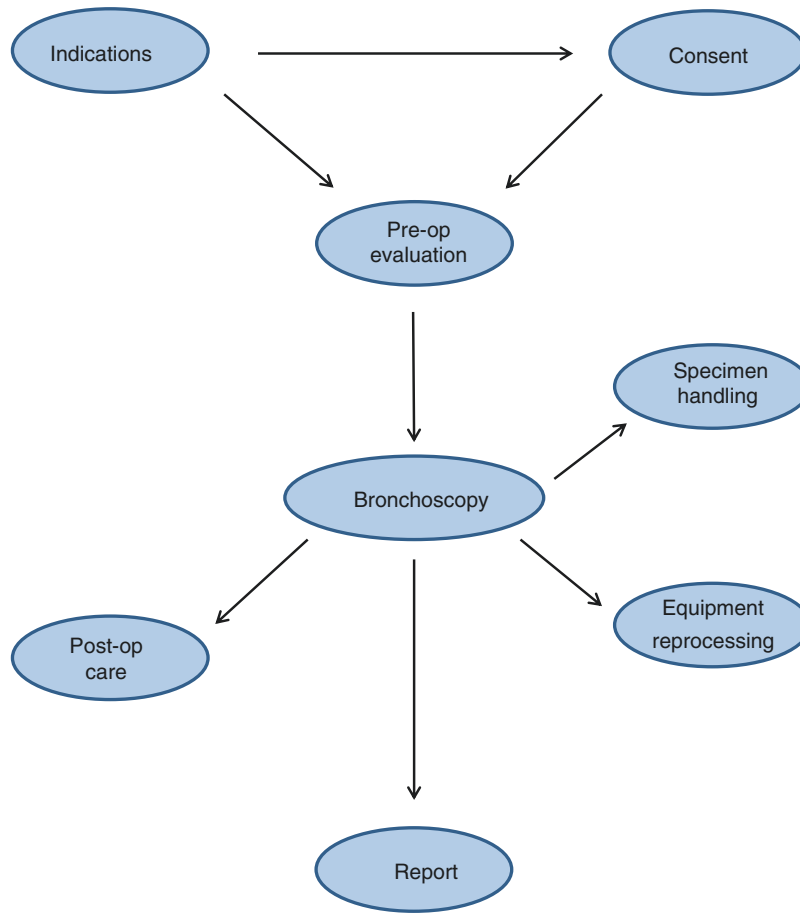

Fig. 14.1 The elements of bronchoscopy

taught. There is no universally accepted curriculum for the teaching of bronchoscopy, but there is a broad consensus as to what bronchoscopists should know before they start performing the procedure independently.

Why Is the Procedure Done?

In contrast with adult bronchoscopy that is geared more and more toward therapeutic applications, the pediatric bronchoscopy remains a primarily diagnostic procedure with a few, for the moment, therapeutic applications (Table 14.1). Several guidelines list a number of symptoms and/or conditions the patient has (e.g., unexplained wheezing, hemoptysis, etc.) as the main indications for the bronchoscopy [2]. Although the symptom is the reason the patient goes to the doctor, the decision to perform FB (versus any other diagnostic test) is based on the expectation that FB may reveal something that other diagnostic or therapeutic modalities cannot. Thus, one can categorize the reasons to perform FB as follows: (a) to determine the presence and severity of anatomical abnormalities (static and/or dynamic), (b) to obtain bronchoalveolar lavage fluid for cultures and other tests, (c) to verify the presence and determine the location of bleeding, and (d) surveillance. The latter is usually done for one or more of the following reasons: (1) detection of occult infection (e.g., many CF centers in other countries advocate annual surveillance bronchoscopies in patients with cystic fibrosis (CF) as part of their routine follow-up), (2) inspection (and biopsy) of a transplanted lung, and (3) evaluation of the condition of a patient with artificial airway(e.g., chronic tracheostomy).

The therapeutic applications of flexible bronchoscopy in pediatrics are very limited by the size and pathology of the pediatric patients. The size of the infant/pediatric airway does not allow the use of bronchoscopes with working channel that is large enough to accommodate specialized equipment such as endobronchial ultrasound (EBUS), lasers, and other therapeutic modalities. In addition, endobronchial lesions that are one of the most common indications for FB in adults are pretty rare in children.

Table 14.1 Indications for flexible bronchoscopy in infants and children

Diagnostic	Therapeutic
Determine the presence and severity of anatomical abnormalities	Persistent atelectasis
Abnormal breathing sounds (e.g., persistent stridor, persistent wheezing)	Foreign body retrieval (if rigid bronchoscopy is not available or if foreign body cannot be reached with the rigid bronchoscope)
Evaluation of suspected or known anatomical abnormality (e.g., tracheoesophageal fistula)	Difficult intubation
Suspected endobronchial lesions and/or foreign body	
Bronchoalveolar lavage (BAL) for:	
Cultures	
Cytology	
Lipid-Laden macrophages/ pepsin assay	
Alveolar proteinosis	
Determining site of bleeding	
Surveillance for	
Airway injury/repair (e.g., smoke inhalation injury)	
Cultures (e.g., in patients with cystic fibrosis)	
Transbronchial biopsies to rule out rejection of transplanted lungs	

The Airways

Flexible bronchoscopy is an exploration of the airways. It is obvious that one cannot determine whether a finding is abnormal without knowing how the normal looks like. Thus, it is imperative for the trainees to learn the normal anatomy of the airways first, then, its normal variants and finally the various abnormalities. Considering that when a patient with a certain airway abnormality may present is totally unpredictable, each program should develop its own library of slides and/or videos. Although the subject (i.e., anatomy) lends itself to the format of a lecture, it is known that listeners absorb only a fraction of

what a speaker is presenting, and they remember even less. The airway anatomy can be best taught (and retained by the trainee) when it is presented in a clinical context. When possible, it is very important to correlate the bronchoscopy findings with radiographic findings, pulmonary function tests (PFTs) and clinical symptoms.

The airway abnormalities can be broadly divided into "structural" and "dynamic". The structural are fixed (e.g., complete tracheal rings and tracheal bronchus) and do not change significantly during the respiratory cycle, whereas the "dynamic" (e.g., tracheomalacia) vary significantly not only during the regular respiratory cycle but especially with changes in the intrathoracic pressure such as during crying or coughing. The primary objective of the diagnostic bronchoscopy is to find an abnormality that can explain the symptom, but it does not necessarily provide a diagnosis by itself. For example, presence of subglottic stenosis can explain persistent stridor but it does not reveal the cause of the stenosis (it could be idiopathic, or secondary to tracheal injury or a manifestation of granulomatous polyangiitis (a.k.a. Wegener's granulomatosis). It is the association of the finding with the clinical history, radiographic, and/or laboratory findings that will lead to the actual diagnosis.

The Bronchoscope

Before performing the procedure, one should become familiar with the tools that are being used. In brief, there are three basic types of flexible bronchoscopes: the fiberoptic, the videobronchoscopes, and the hybrid. From the outside, all types look very similar consisting of the "body or handle" that is shaped as an elongated narrow inverse cone, and a long insertion tube (the "shaft") that is the part that is actually entering the airways. The main difference between them is in the way the image is acquired and processed. In the fiberoptic bronchoscopes, the image is transmitted through glass fibers, directly to an eyepiece located on the top of the head. In contrast, the video- and hybrid-bronchoscopes require a processing unit in order to produce the image [10].

The Body: The wider part of the body is on top. In the pure fiberoptic scopes, the head consists of a round eyepiece with rings that allow focusing (Fig. 14.2). Special adapters also allow cameras to be attached to the eyepiece so one can take pictures or record a video. In the video and hybrid flexible bronchoscopes, the head is a box-like structure without eyepiece (Figs. 14.3 and 14.4). Instead, there are several buttons (in the front and on top of the head) that allow the taking of still pictures, "freeze-frame" and videos. The images are being instantaneously transmitted to a video processor and can be viewed on a video monitor. On the left, all bronchoscopes have a large cable that provides the connection with the light source, and with the video processing unit. In the back of the head, there is a horizontal lever that is articulated on the right side of the head and can move up and down. In the front of the body, there is a suction valve that is covered by a disposable adaptor with a port that connects with the suction tubing that on its other end it connects with an external source of negative pressure. By pressing on the valve, one can apply intermittent or continuous

Fig. 14.2 Flexible fiberoptic bronchoscope

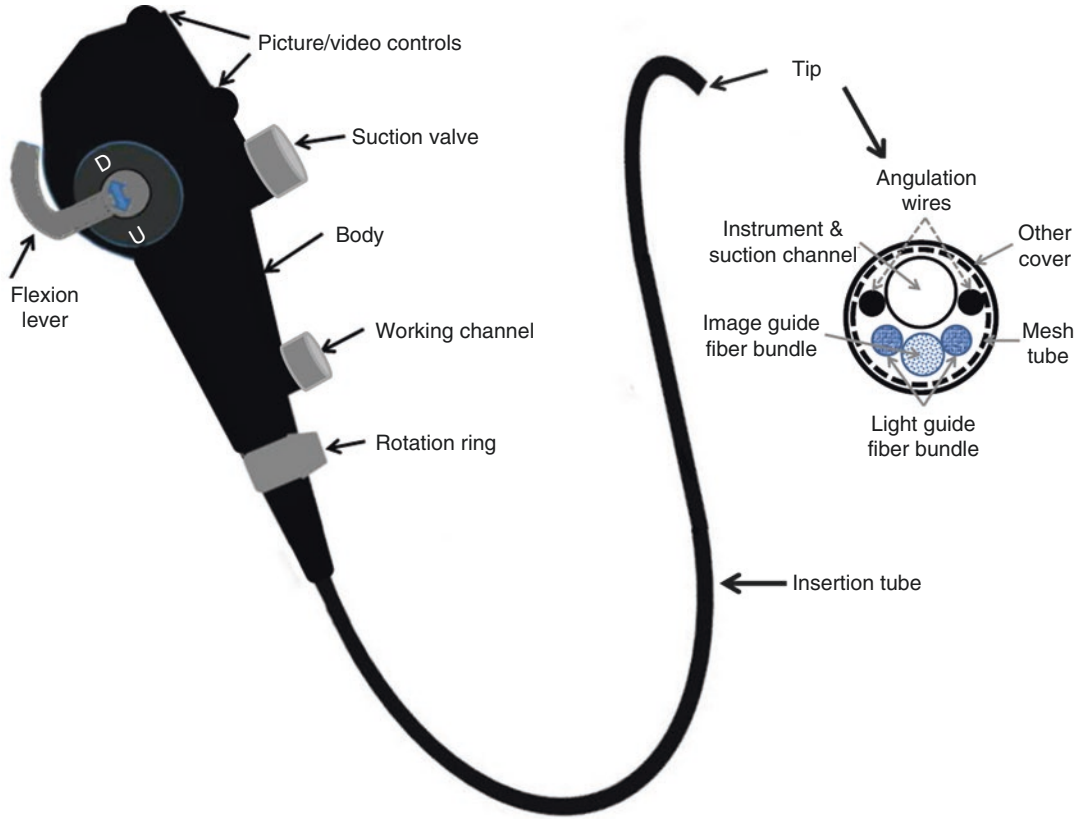

Fig. 14.3 Diagram of a videobronchoscope (side view) with detail of its tip

suction. In the lower part of the body, there is a second valve that connects to the working channel. This valve allows the instillation of fluids (e.g., for bronchoalveolar lavage) and/or the inseryion of instruments (e.g., biopsy forceps). The older fiberoptic scopes had only valve that was serving both as suction and as working channel.

The Insertion Tube: The insertion tube consists of a light metal mesh tube covered by rubber-like material (Fig. 14.3). Inside, it contains several components: There is a channel that starts from the suction valve and runs through the entire length of the insertion tube to its tip, and it is used for suctioning. A second channel starts from the working channel valve, and it is used for instillation of fluid and for instrumentation. The two channels join each other at the lower part of the insertion tube. Thus, there is only one opening seen at the tip. This arrangement saves space, but it has the disadvantage that when an instrument (e.g., brush and forceps) is placed into the working channel it effectively blocks the suction (this is particularly true in the pediatric scopes whose channel is only 1.2 mm in diameter). On the two sides of the suction/instrument channel, there are two wires that are controlling the angulation of the tip of the scope. Below the suction/instrument channel, there is the image guide fiber bundle ("objective lens"). These fibers have to be precisely arranged at both ends of the bundle otherwise the image will be distorted. When they image fibers break the image appears to have dots. On the sides and slightly above the objective lens, there are the light guide fiber bundles that transmit light from the light source.

The diameter of the insertion tube varies from as little as 1.8 to 6.8 mm. The bigger bronchoscopes allow for a bigger channel that in turn

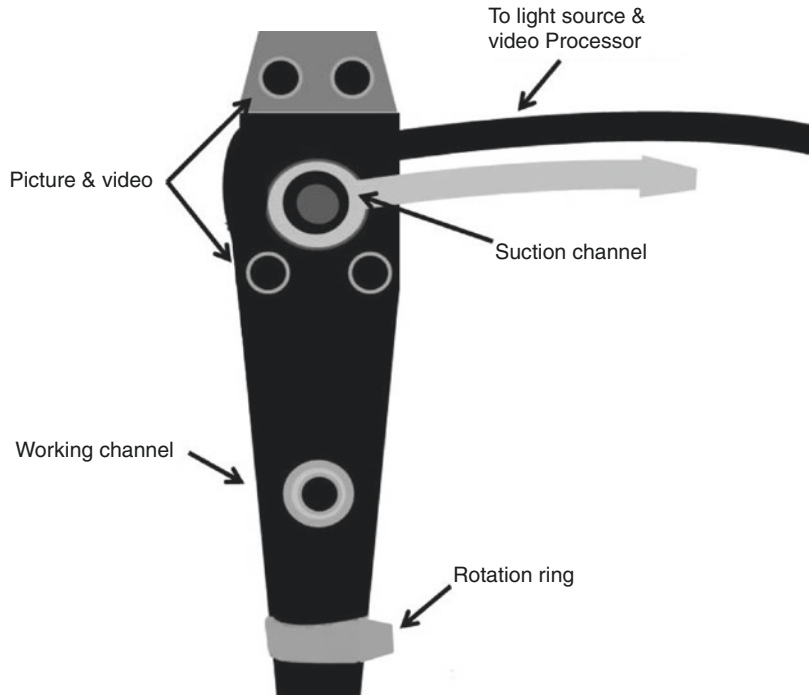

Fig. 14.4 Diagram of a videobronchoscope (front view)

allows the use of more complex instruments. The smallest ultrathin scopes (1.8 and 2.2 mm) do not have suction channels. The channel in all pediatric scopes that are <4 mm in diameter, is 1.2 mm. A 4.0 mm scope can have a 2.0 mm channel, whereas the biggest scopes (>5.5 mm in diameter) can have a channel up to 3.2 mm in diameter. The working length of the insertion tube is 600 mm regardless of the diameter.

Light Source: To be functional, the bronchoscope needs to have a light source to illuminate the lumen that is being examined, and a mechanism to transmit the image to the eyepiece and/or to the video processing unit. Modern bronchoscopes use the "pure white" light that belongs in the cool range of white emitted by LED lights (usually in the 4800–6000 K (Kelvin) range). The light is being transmitted via glass fibers that run through the entire length of the bronchoscope and end at the distal tip [10].

Image Acquisition: In the fiberoptic bronchoscopes, the image is being transported with a bundle of precision fibers from the distal tip to the eyepiece that is in the head of the handle of the bronchoscope. In the video bronchoscopes, the image is transferred to the video processing unit via a chip called Charged Coupled Device (CCD). The chip was initially placed near the tip of the bronchoscope, while in the newer scopes, it is housed in the head of the scope. The light emitted from the light source illuminates the airway and it is reflected back to the CCD that creates an image by converting it into signals for Red, Green, and Blue (RGB). There are two different technologies currently employed. The first is called "RGB sequential" (also known as "black & white" system) and it records the three signals sequentially using a rotation RGB filter. This technique creates images of great quality and it can be miniaturized thus allowing the development of smaller scopes. Its major disadvantage is that if the scope moves too fast in relation to the rotating filter, it may create distortion of the colors referred to the "rainbow effect." The other technology (RGB color chip) is utilizing sensors called pixels (a different one for each color) that record all three colors simultaneously. The method is fast and thus it significantly reduces the "rainbow effect." Its main

disadvantage was its size that prevented its use in small scopes. However, the advances in technology have decreased its size sufficiently and it is now the predominant method for image acquisition in most countries including the USA. Both the color chip and the RGB sequential methods require a video processing unit that receives the signals with wires and converts them into actual image [10].

Movement Control: The bronchoscope is inserted and advanced into the airways manually. The direction is controlled by a horizontal lever that is located on the head of the handle. The lever moves up or down and flexes the tip of the bronchoscope upwards and downwards. The upward angulation in the older flexible bronchoscopes is 180°, whereas in the newer videobronchoscopes, it reaches 210°. The downward angulation is standard at 130° (newer types of disposable bronchoscopes offer increased downward angulation). It should be noted that the lever is moving in the opposite direction of the tip of the bronchoscope (i.e., pushing the lever downwards angulates the tip of the scope upwards and vice-versa). Change of the direction to the left or to the right can be achieved by rotating the shaft of the scope clockwise or counterclockwise. This can be best achieved by creating a "loop" (Fig. 14.5) and holding the shaft gently with the tips of the thumb and the index or middle finger. Attention should be paid that the loop is not tight, so the fibers are not damaged. It is important not to exert pressure and not to attempt to twist the shaft with force. Inexperienced bronchoscopists often twist the shaft as if they are using a screwdriver. This will not only damage the shaft (especially the fibers) but it actually prevents its rotation. As a rule of thumb, if one uses the wrists, especially of the hand that holds the shaft, they are using the bronchoscope the wrong way. On certain occasions such as when using the bigger less flexible bronchoscopes or when the bronchoscope is inserted through an endotracheal tube deep enough, and there is not enough length to create the loop, the shaft can be rotated by rotating the body of the bronchoscope. However, the rotation is limited by the flexion of the wrist of the operator.

Fig. 14.5 Demonstration of the "loop" of the shaft and of the angulation of the tip

In addition, rotation of the head of the scope also rotates the suction and the working channel valves, thus making them inaccessible to the assistant. To minimize these problems, certain newer bronchoscopes are equipped with a ring located at the bottom of the handle that allows partial rotation of the tip of the scope thus facilitating the insertion into areas with sharp angles (e.g., the right upper lobe). It also allows the rotation of the valve of the working channel toward an assistant without changing the position of the handle.

Whether the body of the bronchoscope should be held with the left or the right hand has been a point of debate. Many argue that the fact that the lighting/video cable and the suction tubing originate from the left side of the body, implies that the body should be held by the left hand so the cable and suction tubing are out of the way. Others insist that holding the body with the right hand and the shaft with the left is superior. We believe that the best handling is whichever makes the bronchoscopist comfortable (determined to a large extent by whether the individual is right-handed or left-handed).

Access

The "preferable" entry point of the bronchoscope into the airways remains rather controversial. There are many different routes and very strong opinions in favor or against each one of them. We believe that there are no inherently "good" or "bad" routes and that the selection should be decided on a case-by-case basis. The preferred route should satisfy three basic criteria: (a) to maximize the reliability of the findings, (b) to maximize the safety of the patient, and (c) to maximize the easiness of the procedure. However, the relative importance of these criteria changes from patient to patient in accordance with the indication(s) of the procedure. For example, although an endotracheal tube provides maximal "safety," it is contraindicated when the indication for the procedure is to evaluate stridor in an infant because it completely obscures the extrathoracic airways that are most likely the part of the airways that produces the symptom. On the other hand, an endotracheal tube is acceptable (or preferable) if the indication for the bronchoscopy is to obtain cultures from bronchoalveolar lavage in a patient with diffuse pneumonia. Table 14.2 summarizes the relative usefulness of each route in relation to the indication(s) for the procedure.

Entering the Airways

If one passes the bronchoscope through the nose in a spontaneously breathing individual, the larynx should be visible as soon as the bronchoscope passes the soft palate. However, the view may be obscured by a variety of factors such as large amount of lymphoid tissue, the shape of the epiglottis (the infant epiglottis is Ω-shaped and in a horizontal rather than in an upright position, often almost touching the posterior pharyngeal wall). Collapse of the epiglottis onto the posterior pharyngeal wall can be seen even in a normal person under anesthesia. If a laryngeal mask airway is used, the epiglottis is compressed and flattened, obstructing (partially or completely) the view of the glottis. In such cases, one has to move the bronchoscope slightly downwards in the midline, flexing slightly upwards as soon as the tip is under the epiglottis (the movement resembles using a gardening shovel to unearth a root) and then flexing downwards as soon as the vocal cords are in good view in order to enter into the subglottic space and the upper trachea. Alternatively, one may attempt to enter from the side of the epiglottis. Hyperextension of the neck and occasionally cricoid pressure may be helpful. The glottis and the subglottic space are very sensitive and even when the area has been anesthetized with lidocaine, the touch by the bronchoscope and/or inadvertent suctioning can easily cause laryngospasm that can cause significant problems in oxygenating and ventilating the patient. Thus, one has to go through these structures as fast as possible. In fact, the subglottic space is much easier to inspect as the bronchoscope is being withdrawn. Laryngospasm often resolves spontaneously. If it persists, application of positive airway pressure

Table 14.2 Criteria for the selection of the route of insertion of the bronchoscope relative to the indication(s) for the procedure

	Abnormal breathing sounds			Structure/dynamics of trachea & bronchi			Procedures (bronchoalveolar lavage; biopsies)		
ROUTE	Easiness	Safety	Reliability	Easiness	Safety	Reliability	Easiness	Safety	Reliability
NASAL	+ +	+ +	+ + + + +	+ +	+ +	+ + + + +	+ +	+ +	+ + + + +
LMA	+ + + + +	+ + + +	+ +	+ + + + +	+ + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +
ETT[a]	Not indicated			+ + +	+ + + +	+ +	+ + + +	+ + + +	+ + + + +
T-TUBE[a]	Not indicated			+ + +	+ + + +	+ + +	+ + +	+ + + +	+ + + + +
FACE MASK	+ +	+ + +	+ + + +	+ +	+ + +	+ + + +	+ +	+ + +	+ + + + +
ORAL	+	+ +	+ +	+	+ +	+ +	+ +	+ +	+ + + + +

LMA laryngeal mask airway, *ETT* endotracheal tube, *T-tube* tracheostomy tube

[a]Although endotracheal tubes and tracheostomy tubes are the most secure airways and allow for full ventilation, their effectiveness is often limited because the bronchoscope obstructs a significant portion of their lumen

may relieve it. In rare cases, paralysis with succinylcholine may become necessary.

Upon entering the subglottis, the tip has to be flexed slightly downwards so it stays in the center of the tracheal lumen. Generations of pediatric pulmonary fellows have been trained by hearing the phrase "off the wall" uttered calmly (or screamed) by their instructor. Keeping the bronchoscope in the center of the tracheal lumen is not only for safety purposes (in order to avoid "scratching the tracheal or bronchial wall"). It is also the only way to reliably assess the shape of the trachea, to verify the presence of the tracheal rings only on the anterior wall and not on the posterior wall, to detect external compressions, and to assess the degree of collapse due to malacia. In a normal trachea, one should have a tunnel view of the entire trachea, the main carina, and the take-off of the main stem bronchi.

There is no specific guideline as to whether one should inspect first the right or the left lung. However, developing a specific routine helps one to remember to inspect all the segments. It is also useful, in retracing one's steps during the review of the pictures/videos that were hopefully taken during the procedure. However, if the patient is unstable one should inspect first the area of interest.

There are also no specific guidelines as to whether and how many pictures and/or videos one should take during a bronchoscopy. In the past there were significant practical limitations to picture taking (they were time consuming, they could not be taken by the bronchoscopist but only by an assistant, and they were expensive). The modern bronchoscopes and the digital photography virtually eliminate all these problems. We recommend taking pictures of all lobar and segmental bronchi and, of course, of everything that is or is suspected to be abnormal. Because after the first couple of generations, all airway divisions look very similar, it is very helpful if a record of where exactly each picture was taken is kept. Videos are also very helpful especially for training purposes. While an experienced bronchoscopist can inspect both lungs in less than a minute, a novice bronchoscopist may take much longer to just move the bronchoscope a few millimeters (or not at all). Sometimes, this is because of anxiety that advancing the bronchoscope may cause some damage, or because they are not sure of how to proceed, or because they cannot appreciate the passing of time. In addition, because their concentration is on handling the bronchoscope, they may overlook significant pathology (especially dynamic changes). Reviewing the videos afterwards clearly illustrates the unnecessary delays and allows the instructor to point out areas of interest as well as practical tips.

Although a bronchoscopy is not a race, time is of essence and effort should be made to keep the procedure as short as possible. The duration of a bronchoscopy varies, in part due to the differences in experience and skill among bronchoscopists but also because of the different indications for the procedure. For example, doing a BAL to obtain cultures in a patient with diffuse lung disease can be accomplished very fast because one can lavage the most easily accessible segment. On the other hand, looking for the site of occult bleeding will undoubtedly take much longer time because each and every accessible segment has to be inspected. If and when the concern is about tracheobronchomalacia, it is advisable to wait until the patient coughs so the dynamic collapse can be observed. This means that the anesthesiologist has to let the patient wake-up, something that often may take several minutes.

Other Perioperative Issues

As it was mentioned, a bronchoscopy involves many different elements that a trainee must learn and master. Several of them are being discussed in other chapters of this book. Thus, we briefly discuss only a few.

Consent

The consent for the procedure is both a legal and a medical document. Each hospital has its own forms that have been reviewed by their legal departments and which should be followed as instructed. Despite certain (often stylistic) differences between them, all consent forms cover two major areas. The first is to specify what exactly is to be done to the patient. The second is to explain the possible complications that may develop during and/or after the

procedure so the patient (or the parent/guardian) can be fully informed before giving their approval.

FB is generally a safe procedure when all necessary precautions are taken, but the potential of adverse effects cannot be entirely ruled out. Such complications can be categorized as follows: (a) adverse effects that are minor, very common and largely "unavoidable" (e.g., increased cough and/or sore throat due to pharyngeal and/or laryngeal irritation from the use of a laryngeal mask airway (LMA) or of an endotracheal tube or of the bronchoscope itself; (b) complications that are serious but preventable (e.g., aspiration of large amount of gastric contents can be a very serious adverse effect but a very unlikely one if the patient follows the instructions about restricting food and fluid intake several hours prior to the procedure); and (c) complications that are serious and can potentially happen even when precautions are taken(e.g., transfusion of platelets during the procedure minimizes but does not rule out the risk of bleeding in a patient with active coagulopathy). In general, the consent should inform about all the possible adverse effects that are directly related to the procedure but it is prudent to explain that the likelihood of any of them happening is considerably different depending on the circumstances (for example, a pneumothorax is unlikely to happen during a regular airway inspection, but relatively high after a transbronchial biopsy).

The Bronchoscopy Report

Writing a good bronchoscopy report is almost as important as the procedure itself. It should be detailed, factual, and easily understood by those who read it. It serves as the official document that describes what was done to the patient, by whom and how, and most importantly what was found. There is no universally accepted template for a bronchoscopy report. The software programs provided by the manufacturers of bronchoscopy equipment do provide bronchoscopy reports that auto-populate with the labeling of the pictures. Despite the convenience, they tend to be rich in (often redundant) detail but poor in terms of context (as well as in terms of grammar and syntax). Attempts to modify them into a more readable narrative are rather time consuming and cumbersome. An alternative is for every center to develop their own template in their electronic medical record system.

The report should give an as complete as possible description of the findings. With regard to the procedure, it should specify who participated and their role (e.g., primary bronchoscopist, assistant etc.), the equipment used and the exact procedure(s) done. The amount of detail in describing how the procedure was performed varies among bronchoscopists. Some describe step by step the movement of the bronchoscope. Others (including the author), argue that since there are really very few options as to how to advance the bronchoscope (e.g., the only way to move from the right lung to the left lung is by withdrawing the bronchoscope to the level above the carina), there is usually no reason to describe in excruciating detail how each step was performed. Instead, the emphasis should be on creating a cohesive narrative that starts with the indications for the procedure, the detailed description of the findings and an impression as to whether and to what extent the procedure answered any of the questions that made it necessary in the first place. The findings should address at the minimum the following:

For the Larynx

- Is it structurally normal?
- Is there evidence of laryngomalacia (if yes, which cartilages are involved and how severe is the obstruction)?
- Is there evidence of laryngeal cleft? ("normal" appearance does not rule out presence of a type 1 cleft)
- Are both vocal cords visible? Are they mobile? If not, are they in adduction or in abduction?
- Is the mucosa edematous and/or erythematous?
- Are there any mucosal lesions (e.g., nodules, ulcers, and plaques)?

For the Tracheobronchial Tree

- Are the airways patent?
- Is there any visible narrowing (e.g., subglottic stenosis and/or tracheal stenosis)?
- Are the rings visible in the cartilaginous airways?
- Is there a well-delineated membranous portion?
- Is there external compression and where? If yes, is it pulsatile?
- Are there significant dynamic changes in the airway lumen between inspiration and exhalation, during cough or with suctioning?
- Are there anatomical variations (e.g., tracheal bronchus and right upper lobe with only two instead of three segments etc.)?

(a) *Endobronchial findings*:
Are there any nodes; tumors; foreign bodies; mucus plugs?

(b) *Mucosal appearance*:
The appearance of the mucosa should be described in terms of its (a) color (e.g., erythematous and pale), (b) texture (e.g., smooth, eroded, and atrophied), (c) presence of abnormal lesions (e.g., nodules and ulcers), and (d) friability.

(c) *Secretions*: the secretions should be described in terms of (a) quantity (small or moderate amount; copious); (b) location (diffuse, localized); (c) appearance (clear; hazy, milky, frothy; purulent); (d) consistency (thin, thick); (e) color (white, yellow, green, bloody); mucus plugs.

Ideally, each positive finding should be accompanied by a picture.

If the bronchoscopy does not reveal any abnormalities, one could make a general statement such as "the larynx, trachea, and bronchi were anatomically normal. There were no abnormalities in the mucosa. There was only a small amount of clear secretions". The FB is a procedure that provides evidence supporting or ruling out a certain diagnosis, but it does not provide a specific diagnosis by itself. This should be conveyed in the impression.

Part 2. How Should the Bronchoscopy Be Taught?

Although trainees learning FB are already highly trained physicians, it remains a learning process, and as such, it is subject to education theories about learning. Education specialists distinguish three different types (domains) of learning: the "cognitive learning" in which the trainees acquire knowledge that they can then apply into solving problems; the "psychomotor learning" in which the trainees acquire skills with exposure and practice; and the "affective learning" in which the trainees develop the ability to reliably appraise their own knowledge and work toward further advancement. It is obvious that the bronchoscopy by itself is only a relatively narrow manual skill and as such, it falls primarily into the domain of psychomotor learning. However, learning how to incorporate it into one's practice (why and when to do it) touches the other domains as well.

Generations of bronchoscopists learnt to perform the procedure by observation (i.e., by observing an experienced physician perform it and then attempt to do it by themselves under the guidance of the more senior person. There was very little systematic teaching about all the other elements (indications, consent, perioperative care, etc.) In recent years, several publications have criticized the old "Halsted method" and have promoted more contemporary educational theories, such as Peyton's four-step approach [6–9]. In this, the instructor demonstrates the procedure; then the instructor repeats the procedure but explains step-by-step how it is done; then the instructor repeats the procedure following the trainee's step-by-step instructions; finally, the trainee performs the procedure independently. Although the various published studies show benefits of this approach, they are limited to a one-time teaching and not to a continuous process.

One could argue that the teaching of bronchoscopy is very similar to driver's education.

The latter consists of four parts: (1) a theoretical part that discusses general concepts about cars, describes and discusses the traffic rules, teaches the meaning and significance of traffic signals, and provides a heavy dose of caution for accident prevention; (2) a practical part, during which the student learns the basic processes of driving (how to start the engine, how to hold the steering wheel, how to look at the road, how to make turns, how to park, etc.), but in a controlled environment such as an empty parking lot; (3) the driving, in which the student is actually driving the car under supervision in the traffic; and (4) the evaluation of competence part, in which the student performs certain predefined tasks that if done successfully, convey the license to drive independently. The teaching of bronchoscopy consists of a theoretical part that teaches the anatomy and physiology of the airways, the indications for the procedure and the possible complications. The second part consists of learning how to use the bronchoscope (how to hold it, how to advance it into the airways, how to turn it, and how to "park" it (i.e., wedge it in order to perform a bronchoalveolar lavage). The third part is practice of the first two parts over and over again until the skill is mastered. The fourth step should include the assessment of the trainees' performance that should certify them to perform the procedure independently.

The teaching of bronchoscopy should be a continuum throughout one's fellowship. The theoretical part should be incorporated into the overall teaching of pulmonology. The practical part (i.e., how to use the bronchoscope) has to be taught in the beginning so the trainees can perform it effectively and safely (for the patient and for the bronchoscope). Traditionally, bronchoscopy was learnt by most physicians on patients. This approach (born by necessity) puts severe limitations to the teaching because patients cannot (and should not) undergo repeated (failed) attempts, nor should they be kept under anesthesia for a long time in order to accommodate the teaching part. Fortunately, learning how to hold the bronchoscope, how to angulate the tip and how to rotate it, as well as how to use the suction and the working channel (e.g., threading a biopsy brush or forceps) can be taught without involving a patient.

Navigating the Airways The basic navigation through the airways can be taught (and practiced) on a model of the tracheobronchial tree. The airway models range from totally inexpensive "home-made" ones to multi-thousand-dollar commercial ones usually made by latex. The introduction and popularization of 3-D printing is promising because it could allow the creation of realistic, detailed models based on the appearance of the tracheobronchial tree in a CT scan [11]. One of their negative aspects is that they are usually made by silicone that can be easily torn especially by novice users.

The major advantage of models is that they can be used over and over again, building confidence on the trainee without posing any danger or creating any discomfort to an actual patient. Models can help the trainees improve their coordination, steady their hand and refine the way they angulate and rotate the scope. Models have also a number of disadvantages such as: (a) size: most models have airways whose size is completely out of proportion with the size of the pediatric or infant airways; (b) complexity: many models do not contain divisions beyond the lobar ones; (c) appearance: models cannot present the complex and variable appearance of the pathologic mucosa; (d) lack of dynamic change. This is a very important limitation because the majority of the airway abnormalities in infants and children are due to external compression (e.g., by a vascular ring) and/or due to dynamic changes in the airway lumen (malacia) during the respiratory cycle. These abnormalities are often exaggerated or minimized with changes in the intrathoracic pressure (e.g., bronchomalacia may result in complete collapse of the airway when the patient coughs. Alternatively, the malacia may be underestimated if the patient is mechanically ventilated with high positive end expiratory pressures (PEEP).

Advances in computer technology and graphics have allowed the development of simulation

programs that provide more realistic presentation of the airways and possibly varying scenarios of different pathologies [5, 11–17]. Simulation programs originated in the aviation industry but they have found applications in multiple areas from the military to surgery. Its use in bronchoscopy offers the same benefits with a model (i.e., the ability to practice repeatedly without creating any discomfort or increase the risk for a real patient) but in a much more realistic way and most importantly in an interactive manner. However, simulation has a major disadvantage, namely its cost, that for the advanced versions can run into hundreds of thousands of dollars, something that is prohibitive to virtually any academic program. There is also little incentive for manufacturers to produce specific products for pediatric use because the number of pediatric bronchoscopies is markedly lower than the adult ones. Thus, the use of inexpensive models makes much more sense for most programs. The recognition of the pathology can be taught through video libraries that any program can develop by preserving and editing their own files. From a practical standpoint, we believe that the navigation skills can be acquired and perfected with practice on inexpensive (even "homemade" models).

Duration of Training and Assessment of Competence

The basics of the bronchoscopy can be taught in a very short period of time and this can be accomplished either by one-on-one training or by attending the special workshops or courses that are being offed by professional organizations as well as by individual institutions (e.g., the almost 40-year-old Bronchoscopy course at the Cincinnati Children's Hospital as well as couses and workshops offered by various professional organizations). However, learning the basics does not (or should not) automatically qualify somebody to perform the procedure independently. Currently, there are no specific universally accepted criteria for assessing the competence in bronchoscopy. Virtually every adult and pediatric program base their assessment of the competency of the trainees on quantitative criteria, i.e., how many bronchoscopies a trainee performed during their training (the assumption being that if a trainee has performed a certain number of procedures, he/she has mastered the procedure enough to perform it independently. The number of the minimum bronchoscopies varies, but a general consensus is that trainees in adult Pulmonology need to have performed at least 100 bronchoscopies and 50 procedures with EBUS [18]. In a survey of Pediatric Pulmonology Program Directors [19], the consensus was that 50 bronchoscopies (EBUS cannot be used in infants and small children) would be adequate to qualify somebody to practice independently [4, 20–26]. The difference in the criteria between adult and pediatric programs is rather striking, considering that pediatric bronchoscopies are, if anything, even more challenging than the adult ones. The main reason for the difference is the number of procedures performed during one's training, that are in the thousands in adult training programs but only a few hundred for most pediatric programs. Neither the adult nor the pediatric programs have specific qualitative criteria for the performance of trainees. Thus, there is a movement to move away from the numerical criteria and instead evaluate trainees on their actual performance. At this point, there is no specific metric. We believe that the competency of a trainee should be based on specific metrics based on the following three areas:

A. *The actual procedure*. The trainees should be evaluated on their ability to:
   1. Hold and maneuver the bronchoscope
   2. Navigate through the airways and correctly identify each segment
   3. Number of mistakes (e.g., hitting the wall)
   4. Access difficult bronchi
   5. Ability to perform the FB through different ports of access (nasal; LMA, endotracheal tube; tracheostomy tube)
   6. Complications (e.g., significant desaturations or bleeding)

   The assessment of 1–3 can be done easily in a model; the other three will have to be assessed during the performance of an actual bronchoscopy

B. *The practical aspects of the bronchoscopy*
   1. Choosing the right bronchoscope
   2. Setting up the bronchoscopy cart
   3. Collecting and distributing the specimens
   4. Cleaning/reprocessing the used bronchoscope

C. *The medical aspects of the procedure*
   1. Considering and deciding on the indications for flexible bronchoscopy
   2. Consent
   3. Evaluation & preparation of the patient
   4. Anesthesia and Sedation
   5. The bronchoscopy report (including the verbal communication of the findings to the patient/family)

   The assessment of the first part could be done on a 5-point Likert scale while the other two could be more qualitative (e.g., below expectation, satisfactory, above average). The assessment could be done routinely (ideally after each procedure the trainee performs or quarterly or semiannually) so appropriate feedback can be given.

Summary

Flexible bronchoscopy is an established diagnostic modality and occasionally therapeutic modality in the care of children with a variety of respiratory disorders. FB involves both manual skills and theoretical components that should be incorporated into the trainees' overall knowledge of pulmonary medicine. The teaching of the procedure is still lacking a specific curriculum as well as standardized methods of assessing the trainees' competency.

References

1. Miller RJ, Casal RF, Lazarus DR, Ost DE, Eapen GA. Flexible bronchoscopy. Clin Chest Med [Internet]. 2018 Mar 1 [cited 2018 Dec 23];39(1):1–16. Available from: https://www.sciencedirect.com/science/article/pii/S0272523117300904?via%3Dihub.
2. Faro A, Wood RE, Schechter MS, Leong AB, Wittkugel E, Abode K, et al. Official American thoracic society technical standards: fFlexible airway endoscopy in children. Am J Respir Crit Care Med. 2015;191(9):1066–80.
3. Schramm D, Yu Y, Wiemers A, Vossen C, Snijders D, Krivec U, et al. Pediatric flexible and rigid bronchoscopy in European centers—availability and current practice. Pediatr Pulmonol. 2017;52(11):1502–8.
4. Stather DR, Jarand J, Silvestri GA, Tremblay A. An evaluation of procedural training in Canadian respirology fellowship programs: program directors' and fellows' perspectives. Can Respir J. 2009;16(2):55–9.
5. Stratakos G. Contemporary bronchoscopy training and assessment: a la recherche du professionnalisme perdu? Respiration. 2012;83(2):101–2.
6. Romero P, Günther P, Kowalewski KF, Friedrich M, Schmidt MW, Trent SM, et al. Halsted's "see one, do one, and teach one" versus Peyton's four-step approach: a randomized trial for training of laparoscopic suturing and knot tying. J Surg Educ [Internet]. 2018;75(2):510–5. Available from: https://doi.org/10.1016/j.jsurg.2017.07.025.
7. Burgess A, Oates K, Goulston K. Role modelling in medical education: the importance of teaching skills. Clin Teach. 2016;13(2):134–7.
8. Münster T, Stosch C, Hindrichs N, Franklin J, Matthes J. Peyton's 4-steps-approach in comparison: medium-term effects on learning external chest compression - a pilot study. GMS Z Med Ausbild. 2016;33(4):Doc60.
9. Nikendei C, Huber J, Stiepak J, Huhn D, Lauter J, Herzog W, et al. Modification of Peyton's four-step approach for small group teaching - a descriptive study. BMC Med Educ. 2014;14:68.
10. Ernst A, Herth FJF. Principles and practice of interventional pulmonology. New York: Springer; 2013. p. 1–757.
11. DeBoer EM, Wagner J, Kroehl ME, Albietz J, Shandas R, Deterding RR, et al. Three-dimensional printed pediatric airway model improves novice learners' flexible bronchoscopy skills with minimal direct teaching from faculty. Simul Healthc J Soc Simul Healthc [Internet]. 2018;1. Available from: http://insights.ovid.com/crossref?an=01266021-900000000-99601.
12. Myer CM, Jabbour N. Advanced pediatric airway simulation. Otolaryngol Clin North Am [Internet]. 2017;50(5):923–31. Available from: https://doi.org/10.1016/j.otc.2017.05.004.
13. Veaudor M, Gérinière L, Souquet PJ, Druette L, Martin X, Vergnon JM, et al. High-fidelity simulation self-training enables novice bronchoscopists to acquire basic bronchoscopy skills comparable to their moderately and highly experienced counterparts. BMC Med Educ. 2018;18(1):1–8.
14. Yiasemidou M, Gkaragkani E, Glassman D, Biyani CS. Cadaveric simulation: a review of reviews. Ir J Med Sci. 2018;187(3):827–33.
15. Celentano V. Need for simulation in laparoscopic colorectal surgery training. World J Gastrointest Surg [Internet]. 2015;7(9):185. Available from: http://www.wjgnet.com/1948-9366/full/v7/i9/185.htm.

16. Di Domenico S, Simonassi C, Chessa L. Inexpensive anatomical trainer for bronchoscopy. Interact Cardiovasc Thorac Surg [Internet]. 2007;6(4):567–9. Available from: https://academic.oup.com/icvts/article-lookup/doi/10.1510/icvts.2007.153601.
17. Cocciante AG, Nguyen MN, Marane CF, Panayiotou AE, Karahalios A, Beer JA, et al. Simulation testing for selection of critical care medicine trainees a pilot feasibility study. Ann Am Thorac Soc. 2016;13(4):529–35.
18. Lamb CR, Feller-Kopman D, Ernst A, Simoff MJ, Sterman DH, Wahidi MM, et al. An approach to interventional pulmonary fellowship training. Chest [Internet]. 2010;137(1):195–9. Available from: https://doi.org/10.1378/chest.09-0494.
19. Leong AB, Green CG, Kurland G, Wood RE. A survey of training in pediatric flexible bronchoscopy. Pediatr Pulmonol. 2014;49(6):605–10.
20. Eber E, Antón-Pacheco JL, de Blic J, Doull I, Faro A, Nenna R, et al. Achieving competency in bronchoscopy: challenges and opportunities. Theatr Res Int. 2017;50(6):17–9. Available from: https://doi.org/10.1183/13993003.00901-2017.
21. Yarmus L, Feller-Kopman D, Imad M, Kim S, Lee HJ. Procedural volume and structure of interventional pulmonary fellowships: a survey of fellows and fellowship program directors. Chest [Internet]. 2013;144(3):935–9. Available from: https://doi.org/10.1378/chest.12-3028.
22. Voduc N, Dudek N, Parker CM, Sharma KB, Wood TJ. Development and validation of a bronchoscopy competence assessment tool in a clinical setting. Ann Am Thorac Soc. 2016;13(4):495–501.
23. Mahmood K, Wahidi MM, Osann KE, Coles K, Shofer SL, Volker EE, et al. Development of a tool to assess basic competency in the performance of rigid bronchoscopy. Ann Am Thorac Soc. 2016;13(4):502–11.
24. Ost D, Eapen GA, Jimenez CA, Morice RC. Improving procedural training and certification in pulmonary medicine. Chest [Internet]. 2010;137(1):6–8. Available from: https://doi.org/10.1378/chest.09-1281.
25. Melchiors J, Petersen K, Todsen T, Bohr A, Konge L, von Buchwald C. Procedure-specific assessment tool for flexible pharyngo-laryngoscopy: gathering validity evidence and setting pass–fail standards. Eur Arch Otorhinolaryngol [Internet]. 2018;275(6):1649–55. Available from: https://doi.org/10.1007/s00405-018-4971-y.
26. Fielding DI, Maldonado F, Murgu S. Achieving competency in bronchoscopy: challenges and opportunities. Respirology. 2014;19(4):472–82.

Forty-Nine Ways to Get the Wrong Answer from a Bronchoscopy

15

Robert E. Wood

Bronchoscopy is an important aspect of the practice of pediatric pulmonology. The ability to examine and sample the airways of a child adds immeasurably to the diagnostic accuracy and appropriateness of therapeutic measures subsequently employed. Bronchoscopy is a serious procedure that should not be undertaken for trivial reasons, but on the other hand, it is very likely underutilized in contemporary pediatric pulmonary practice. Care must be taken to perform the procedure safely and properly. While every human activity entails some degree of risk, and bronchoscopy is no exception, the incidence of complications of flexible bronchoscopy in pediatric patients is gratifyingly low. However, a more subtle complication is cognitive: *Other than death of the patient, the most serious complication of a diagnostic bronchoscopy is to have done the procedure, and gotten the wrong answer.*

There are many ways to get the wrong answer from a diagnostic bronchoscopy. The following discussion is based on nearly 50 years of doing bronchoscopies and observing my colleagues doing bronchoscopies.

1. Not knowing what you are looking for: A bronchoscopy is always a search for specific information. Clearly, there must be a specific indication for the procedure. If the physician performing the bronchoscopy is not the primary managing pulmonologist, there is a significant potential for missing things if there is no very clear and complete communication in advance of the procedure. "If you don't know where you are going, you are very likely to wind up somewhere else…"
2. Not knowing the history of the patient may cause you to order the wrong lab studies or to overlook pathology you would otherwise have identified. We typically do not order mycobacterial studies on pediatric bronchoalveolar lavage (BAL) specimens, for example, but if we are aware of a pertinent history, this might be a crucial aspect of the bronchoscopy.
3. Not looking at relevant radiographs prior to the procedure may cause you to sample the wrong portion(s) of the bronchial tree. The right middle lobe and the lingula are often cited as the "preferred" sites for BAL, but we must not forget Sutton's Law – "go where the money is." Some years ago, a patient of mine, a lung transplant recipient, came in with a left lower lobe pneumonia. The transplant team decided (I was out of town) to perform a bronchoscopy to guide subsequent therapy. Assuming that the boy had uniform disease, the pulmonologist lavaged the right middle lobe only; the cultures were sterile and the BAL cytology revealed no signs of

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*,
Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_15

inflammation. Several hours later, I returned from my journey, and repeated the bronchoscopy. The BAL from the left lower lobe grew >10,000,000 cfu/ml of Burkholderia cepacia and the cytology revealed a pure exudate. This bronchoscopist not only failed to look at the radiographs but also violated a number of the other points in this essay – the erroneous result could have led to the death of the patient. After all, we had "proven" that the child did not have bacterial pneumonia, by doing the most definitive test – a bronchoscopy! Therefore, the conclusion was that antibiotics were not needed.

4. Not understanding that the patient may be immunodeficient may cause you to order the wrong BAL assays. Typically, we do not order every possible assay on routine bronchoscopies, but in immunocompromised patients, special studies may be crucial.
5. Not understanding that the patient may be neutropenic may cause you to believe that pathogens identified in BAL culture are inconsequential, since there are no polymorphonuclear neutrophils (PMNs) in the BAL. I have established a new diagnosis of an immune deficiency in at least three patients who had pathogens but no neutrophils in the BAL specimen.
6. Obtaining the BAL from the wrong place: Sutton's law.
7. Not examining the entire bronchial tree: Patients often have more than one abnormality or more than one foreign body (fragments). It can be very easy to miss important abnormalities if the entire bronchial tree is not examined. When I am called to perform a bronchoscopic intubation, I always take a few seconds to examine the entire bronchial tree, and in a very substantial percentage of the patients, I find something of importance. Especially in this setting, clearing the bronchi of obstructing secretions can make the subsequent anesthetic session safer for the patient. And if you do aspirate mucus plugs, etc., in this situation, the aspirated material should, at the very least, be cultured. Give the patient the full benefit of the procedure.
8. Using sedation that is too deep may cause you to miss important dynamic abnormalities or to over-diagnose. Flexible bronchoscopy is often employed (as it should be) in the evaluation of children with stridor. Stridor is always visible; if the noise can be heard but the vibrating structures are not seen, the only possible explanation is that the wrong part of the airway is being visualized. Conversely, in a patient with a history of noisy breathing, the examination must be performed under conditions that reproduce the noise. Deep sedation, with low inspiratory flow rates, is very likely to result in a failure to understand the patient's physiology. It is often most useful, I have found, to perform the dynamic aspect of the bronchoscopy after obtaining the BAL specimen (see below for an expansion on this concept), then lighten the sedation to allow a more careful evaluation of the airway dynamics. This applies to the upper and to the lower airways. If the sedation is too deep, it is also possible to make a false-positive diagnosis – the observed dynamic abnormalities must correspond to the clinical history. It is not unusual to find what appears to be very impressive glossoptosis in a child with no history of obstructive sleep apnea (OSA). This may be a false-positive finding, induced by sedation, or it could also be that the history is incomplete (parents of teenagers often are not aware of the symptoms of OSA and wonder why the child is sleepy during the day).
9. Using sedation that is not deep enough may cause you to not see much of anything or to terminate the procedure prematurely. The advantage of having the assistance of an experienced pediatric anesthesiologist is that the level of sedation can be titrated with short-acting drugs. To terminate a procedure because of inadequate sedation is an invitation to missed diagnoses. Change the level of sedation, then complete the examination.
10. Using a laryngeal mask airway (LMA) for routine bronchoscopy will cause you to completely bypass the upper airway and miss a lot of pathology. This, unfortunately, in my

not-so-humble opinion, is the cause of many erroneous diagnoses in pediatric patients. Unless there is a valid reason otherwise (and "unstable upper airway obstruction" is not one of them, since in that case, it is mandatory to evaluate the upper airway and definitively explain the causes of the obstruction if they are not already well defined by a prior procedure), the flexible bronchoscope should be passed transnasally – the airways begin *at the nostril*.

11. Using an endotracheal tube (ETT) for routine bronchoscopy will cause you to completely bypass the upper airway and miss a lot of pathology. Ditto from the LMA (#10 above).
12. Not using an ETT when the primary indication for the procedure is to obtain BAL cultures in an immunocompromised or a patient with cystic fibrosis (CF). Passing a flexible bronchoscope through the native upper airway can lead to contamination of the subsequent BAL specimen, if suctioning is done in the process of reaching the BAL site. Most bronchoscopies performed in immunocompromised patients are done purely for the BAL data, and the anatomy and dynamics of the upper airway are not at issue. Every measure possible should be taken to obtain as clean a specimen as possible. In a supine patient, there is a 30° downhill slope from the larynx to the carina, and oral secretions can and do slide down the trachea with great alacrity. Visualize the giant ski jump at the Winter Olympics.
13. Using positive-pressure ventilation when evaluating for dynamic problems: This will mask tracheomalacia and bronchomalacia, especially if positive end-expiratory pressure (PEEP) is involved as well. A subtle variation on this is the expiratory resistance produced by the presence of the bronchoscope in an artificial airway ("inadvertent PEEP").
14. Not observing the patient cough when evaluating for dynamic problems – may cause you to miss significant dynamic collapse. The visual evaluation of airway dynamics is imprecise at best, and the evaluation of tracheomalacia is often challenging. Many patients who have a history of symptoms such as exercise-induced asthma (EIA), recurrent croup, or a deep brassy sounding cough may demonstrate significant dynamic collapse only during vigorous expiratory effort, especially a cough. Insisting on having the patient light enough to see cough will drive anesthesiologists crazy, and is best done at the end of the procedure, lightening the sedation in preparation for awakening the patient, but before removing the bronchoscope from the airways.
15. Not clearing secretions to see the anatomy clearly enough: Your mother taught you how to vacuum clean, so do it! ☺.
16. Allowing the patient to aspirate saliva prior to obtaining BAL specimen: Take every reasonable measure to get an uncontaminated specimen; start as soon after induction of sedation as possible, and go straight to the preselected BAL target area – see #12 above. It is useful to start the procedure with a deeper level of sedation, rapidly reach the BAL target, and then examine the airway anatomy and dynamics more leisurely, when suctioning can be performed without worrying about contaminating the BAL specimen.
17. Not understanding that a "protected brush" specimen does not eliminate contamination from upper airway secretions aspirated during the procedure. These devices are rarely used in pediatric practice, but are standard procedure in adult patients. They will enable one to obtain a specimen uncontaminated by things suctioned through the bronchoscope prior to passing the brush, but all too often the specimen collected is a representative sample of what has been aspirated during the procedure.
18. Using a flexible instrument when a rigid instrument is more appropriate/effective: Flexible instruments are very limited in their ability to accurately evaluate the posterior aspects of the larynx and subglottic space. Specifically, one cannot manipulate the tissue in such a way as to definitively demonstrate minor laryngoesophageal clefts

(a surprisingly common finding in children with a history of aspiration). I have even had difficulty finding Type II or even Type III clefts, knowing they were there, with a flexible scope. In any child suspected of aspiration, rigid laryngoscopy rather than flexible laryngoscopy is much more likely to yield an accurate anatomic diagnosis.

19. Using a rigid instrument when a flexible instrument is more appropriate/effective: This is especially true of the upper airway dynamics. It is extremely difficult, if not impossible, to evaluate glossoptosis, for example, with a rigid instrument. Most other dynamic upper airway abnormalities are much more readily evaluated with a flexible scope passed transnasally.
20. Failing to use both rigid and flexible instruments when both are needed: Consider the entire spectrum of questions the proposed procedure is tasked to address. Analysis of a BAL specimen is often crucial to effective management (e.g., infection, inflammation, and aspiration), and it is very challenging to obtain a good BAL specimen with a rigid bronchoscope.
21. Failing to examine peripheral bronchi: In many patients, the pathology may lie in fifth-generation bronchi or beyond. If the examination is limited to segmental bronchi, much can be missed.
22. Contaminating the bronchoscope during passage through the upper airway: Do not attach the suction line to the bronchoscope until the tip of the instrument is near the preselected BAL site. It can also be useful to insufflate oxygen through the suction port continuously until the tip of the bronchoscope reaches the carina (2–3 lpm). Obviously, one *should not* wedge the tip of the bronchoscope in a peripheral bronchus while insufflating, as pneumothorax may occur. But the use of oxygen insufflation can be helpful also to distend soft tissue in the nasopharynx or around the larynx, and it also benefits the patient's oxygenation.
23. Not performing the bronchoscopy when it should be done: Physicians may be reluctant to perform a procedure such as flexible bronchoscopy, perceiving the cost/risk/inconvenience to outweigh the potential benefit. In at least two-thirds of patients in whom I initially declined to do a bronchoscopy, subsequently, I discovered my mistake and found significant pathology when I finally did so.
24. Not performing a BAL when it was needed: Just because the airways look "clean," it does not mean that a BAL will be normal. Clearly, a BAL is not needed with *every* flexible bronchoscopy, but before deciding not to do so, the bronchoscopist should think carefully about the global clinical picture of the patient, and err on the side of conservatism by obtaining and analyzing a BAL sample.
25. Not recognizing the anatomy" *Res ipsa loquitur.*
26. Not recognizing the pathology: Airway pathology can be subtle. I am frequently asked to help evaluate a suspected airway problem on the basis of photographic images obtained during a bronchoscopy at another institution. While sometimes I can help, I must point out that a still image of a bronchoscopic finding is vastly inferior to a video recording, which gives multiple images as well as much better perspective.
27. Failing to take the proper specimen (biopsy, brushing) for the observed pathology: However, one must carefully assess risk/benefit in the given situation. Transbronchial biopsy in pediatric patients results in very small specimens with an associated high risk of hemorrhage – my lung transplant surgeon often claimed, "unless you get 100 ml of blood with a transbronchial biopsy, you probably don't have an adequate tissue specimen." I am sure he was exaggerating *a bit*, but if a sample of tissue is needed, carefully consider all the options and choose the most likely option to result in a diagnosis with the least risk. Endobronchial biopsies are much safer than transbronchial, and the pediatric pulmonologist should not be unwilling to do them unless there appears to be a high risk of hemorrhage. Bronchial brushings are relatively very safe, but of limited diagnostic

utility in pediatric patients (except for the evaluation of suspected primary ciliary dyskinesia). To avoid losing most of the specimen, bronchial brushings should be done with the bronchoscope passed through an endotracheal or tracheostomy tube, and the brush should not be withdrawn into the tip of the bronchoscope.

28. Assuming that the pathology is uniform throughout the lungs: You may often need to obtain BAL specimens from multiple locations. Several studies have shown markedly different bacterial flora and cytologic results on BAL specimens taken from multiple sites in the same patient on the same procedure. See also #3 above.
29. Failure to make and keep a video recording of the procedure for future reference: Video recording is crucial! See #30. I have sometimes discovered a significant anatomic abnormality upon review of the video recording (in one case, 1 year later) that I did not appreciate at the moment, during the procedure. For consultation, for teaching, and for comparing findings with those from a previous bronchoscopy on the same patient, a video recording is essential. At CCHMC, every endoscopic procedure is recorded and stored in an online accessible video database, going back to 2006. This video archive is of inestimable value in patient care. I have also testified in several medicolegal cases in which, had the bronchoscopist merely been able to present a video of the procedure, the lawsuit would have been dismissed immediately.
30. Forgetting what was seen before documenting in the patient's medical record: This is all too common! Even the most experienced bronchoscopist – and I surely include myself in this – can (and will) forget the details of the endoscopic findings if the written procedure report is not generated immediately after completion of the procedure (and sometimes even then ☹).
31. Using the wrong technique for BAL: The volume of saline used for BAL must be sufficient to ensure that at least some of the fluid recovered represents alveolar surface liquid. Clearly, too little volume can lead to erroneous results. The only problem is that it is never absolutely clear just what volume is needed. If the tip of the bronchoscope is gently wedged into the bronchus, presumably most if not all of the lung volume distal to that point will be included in the sampling. However, the bronchial generation into which the scope can be wedged is dependent on two major factors: the size of the patient and diameter of the bronchoscope. One might also add the enthusiasm with which the bronchoscopist "wedges" the scope. Problems can also arise when withdrawing the instilled fluid, especially in patients with readily collapsible bronchi (bronchomalacia). When the volume returned is small in proportion to the volume instilled, most of the fluid may represent "dead space" and the specimen may be significantly diluted, sometimes to the point of becoming uninterpretable.
32. Failure to properly interpret BAL data: The pediatric bronchoscopist must ensure that the cytopathologist studying the specimen performs the appropriate stains and interprets the data properly, in the context of the patient's history and the endoscopic findings. In a hospital with a small pediatric presence, the cytopathologist may only be accustomed to dealing with specimens from adults, and may review the slides and report "no malignant cells identified" – full stop. The bronchoscopist should make friends with the cytopathologist and review slides together, at least until there is mutual confidence in the validity and consistency of the interpretations. The bronchoscopist and pathologist can educate each other in the process.
33. Failure to interpret BAL data in the context of the patient's history and the procedural details: The absence of lipid laden macrophages does not mean the patient is not aspirating, especially if the patient is being fed via gastro-jejunal (GJ) tube, for example. If a patient has been given antibiotics just prior to the procedure, there may be detectable levels of the antibiotic in the BAL specimen.

34. Failure to process the BAL specimen promptly: Bacteria die or multiply, and cells die or adhere to the walls of the specimen container. If the specimen is delivered to the laboratory after hours, and sits on a shelf (or even in a refrigerator) overnight, the final results may be very different than that from a fresh specimen.
35. Not getting the BAL specimen to the proper laboratory: The analysis will not get done in a timely fashion.
36. Not getting the BAL specimen to the laboratory at all: *res ipsa loquitur.* Do not depend on the hospital courier system; if in doubt, take it to the lab yourself!
37. Allowing a trainee to do the procedure while not paying close attention: The tip of the bronchoscope can flip from one lobe to another in the blink of an eye, and result in obtaining specimens from the wrong anatomic location, etc.
38. Using an instrument that is damaged.
39. Using an instrument that has not been properly cleaned: There have been mini-epidemics caused by improper cleaning of instruments. There have also been mini-pseudo-epidemics, where the specimens were contaminated, but not the patient, again, due to improper cleaning.
40. Not completing the procedure because of perceived difficulties: You may need to stop, allow the patient to settle down, or even to intubate the patient. Unless there is a legitimate danger to the life of the patient, it should always be the rule that the goals of the procedure are accomplished before terminating.
41. Failure to alter the conditions of the procedure if the dynamic observations are inconsistent with the patient's history (i.e. history of stridor, but no audible stridor during the procedure).
42. Evaluating the upper airway dynamics with the head/neck in the wrong position: Even a very small change in the angle of the neck or elevation of the mandible can have dramatic effects on the airway dynamics.
43. Evaluating the upper airway dynamics with the wrong level of inspiratory effort: Often, impressive laryngomalacia is not seen until the patient is breathing much more vigorously.
44. Applying excessive topical anesthesia to the larynx, thereby causing aspiration of oral secretions: This is one of the reasons why, when doing multidisciplinary procedures (i.e., both rigid and flexible bronchoscopy), the flexible bronchoscopy should be done first. The laryngotracheal anesthesia (LTA) typically employed by the rigid bronchoscopists usually involves instilling 4–5 ml of lidocaine into the trachea and hypopharynx; this is guaranteed to wash a considerable amount of oral secretions into the trachea and bronchi.
45. Performing the flexible bronchoscopy after rigid endoscopy (the delay and manipulation allow aspiration of oral secretions – See #44).
46. Using a bronchoscope of the wrong size: Larger scopes obstruct more of the airway and limit correct interpretation of dynamics and reduce the potential to visualize more peripheral bronchi. Larger bronchoscopes, with larger suction channels, may result in more mucosal trauma, with bleeding, and also may confuse the interpretation of airway dynamics.
47. Doing the bronchoscopy at the wrong time: Sometimes, it may be most informative to do the bronchoscopy when the patient is ill, rather than wait until recovery.
48. Doing the bronchoscopy after the patient has been given antibiotics: False-negative cultures.
49. Failure to obtain ancillary data (i.e., to do a bronchogram, or a simultaneous esophagoscopy).

I am certain that there are many other ways to get the wrong result from a diagnostic bronchoscopy, but these points are offered to lead the reader to perform the most important aspect of bronchoscopy – THINK!

Part II

Role of Flexible Bronchoscopy in Evaluation of Pediatric Respiratory Tract Disorders

16 Approach to Common Chief Complaints

Howard B. Panitch

Introduction

Some of the most frequent indications to perform airway endoscopy in children include noisy breathing, chronic wheezing unresponsive to therapies for asthma, and chronic cough [1, 2]. The decision to perform bronchoscopy is based on a combination of several factors, including history and physical examination findings, impact of the problem on the child's health and well-being, results of prior studies, anticipation of how the information gained will affect future care of the patient, and understanding of the natural history of the problem. For instance, flexible bronchoscopy might be delayed or avoided in an infant with intermittent vibratory stridor who is growing and developing normally, since the likelihood that the infant would outgrow the problem without intervention is high. In contrast, bronchoscopy is warranted in an infant with vibratory stridor who has feeding difficulty, poor growth, and episodes of apnea.

Several reviews report excellent diagnostic efficiency of flexible bronchoscopy [3–7]. When evaluating children with noisy breathing or wheezing, the examination involves anatomic or structural assessment as well as observation of airway dynamics [8]. The latter is state dependent; some problems arise only during sleep while others might occur only with exercise. Thus, accurate diagnosis requires a recognition of the conditions under which the problem exists and an understanding of how the airways behave under normal and pathologic conditions. Ideally, those conditions can be reproduced during the examination so that the cause of the problem can be identified. Equally as important, dynamic findings that do not correlate with the child's presentation can be ignored. For instance, dynamic collapse of supraglottic structures after anesthesia or after administration of topical lidocaine in a child with no history of stridor is most likely a reflection of the effect of the anesthesia and does not reflect a pathological condition [9–11]. Similarly, tracheal collapse noted endoscopically during coughing or crying in an infant with no history of wheezing reflects normal airway dynamics [12, 13] and should not be labeled as tracheomalacia.

Airway Dynamics: General Considerations

While the airways serve as a conduit for gas exchange between the atmosphere and alveoli, they are not rigid tubes: they are exposed to transmural pressures ($P_{tm} = P_{intraluminal} - P_{pleural}$ for

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_16

intrathoracic airways and $P_{intraluminal} - P_{atmospheric}$ f or extrathoracic airways) that cause changes in length and width with each respiratory cycle (Fig. 16.1). Inside the thorax, intrapleural pressure becomes more negative during inspiration, causing a relative positive transmural pressure that results in lengthening and widening of the intrathoracic airways as a subject inhales. During exhalation, the pleural pressure is greater than intraluminal pressure and so the airways shorten and narrow. The opposite occurs above the sternal notch, in the extrathoracic airway. There, atmospheric pressure (considered 0 cmH_2O) is more positive than intraluminal pressure during inspiration, causing the extrathoracic airway to narrow during that phase of breathing. During exhalation, intraluminal pressure in the extrathoracic airway is higher than atmospheric, and so the airway dilates slightly. These relationships explain why signs and symptoms of extrathoracic obstruction are accentuated on inspiration, while those of intrathoracic obstruction are more prominent on exhalation.

The normal change in airway cross-sectional area that occurs with change in transmural pressure will also be accentuated if transmural pressure increases. Thus, if an infant uses abdominal accessory muscles to exhale because of peripheral airway obstruction, transmural pressure across the central airways will be more positive than at rest and the airway may appear collapsible. Alternately, if a subject is heavily sedated and breathes with a shallow pattern, transmural pressure across the airway wall will be minimized and significant collapse can be overlooked.

The relative change in airway caliber is determined not only by the direction and magnitude of the transmural pressure across it but also by the characteristic stiffness of the airway wall. The trachea and main bronchi are comprised of C-shaped cartilages whose tips are spanned by a membrane of contractile and connective tissue. The cartilage is fairly stiff, but the posterior membrane is not as stiff and can invaginate into the lumen or evaginate depending on the direction and magnitude of the transmural pressure. The pressure–volume

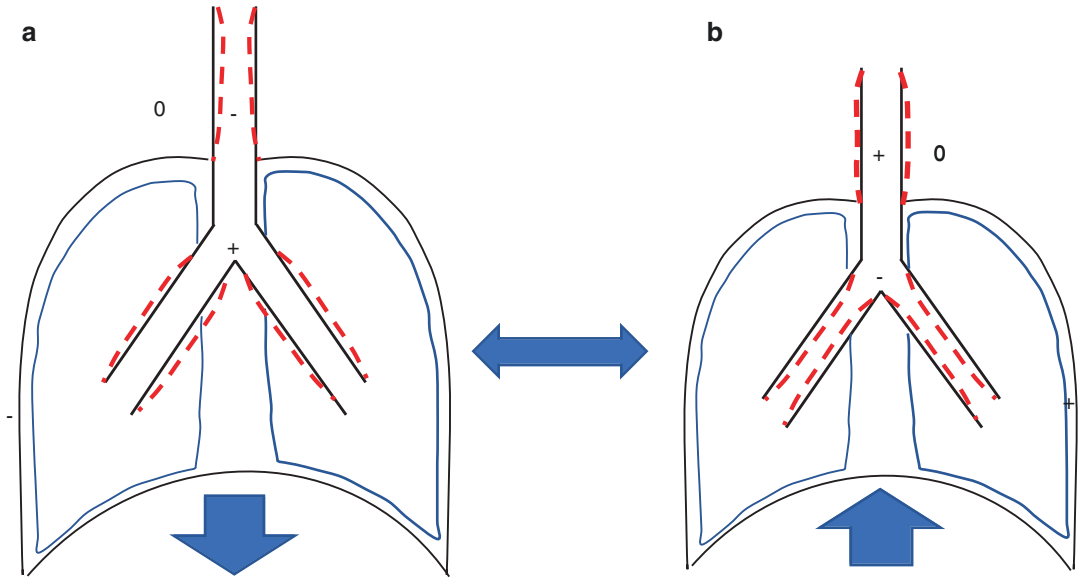

Fig. 16.1 (**a**) During inspiration, pleural pressure becomes more subatmospheric to draw air into the alveoli. Within the thorax, pleural pressure is lower than pressure within the airway lumen. As a result, transmural pressure (P_{TM}) acts as a distending force to dilate the intrathoracic airways. In the extrathoracic airway, intraluminal pressure falls below atmospheric pressure, so that P_{TM} favors narrowing of the extrathoracic airway. (**b**) During exhalation, pleural pressure becomes more positive than intrathoracic intraluminal pressure, resulting in narrowing of the intrathoracic airway. In the extrathoracic airway, however, intraluminal pressure is greater than atmospheric pressure, so that the extrathoracic airway dilates

relationship, or compliance of the airways changes with maturation. Tracheae from newborns are more compliant than those of infants and children, which in turn are more compliant than those of adults [14]. The increase in stiffness involves both the cartilaginous and contractile components of the airway wall [15, 16]. Thus, under normal circumstances, for the same change in transmural pressure the airway of a younger subject will have greater changes in cross-sectional area than that of an older one. The tone of airway smooth muscle also impacts on airway stiffness: contraction of the trachealis muscle will stiffen the airway and prevent collapse, while relaxation of airway smooth muscle can enhance the collapsibility of the central airway [17–19].

In addition to pressure across the airway wall, one other set of pressures that must be considered when assessing airway dynamics relates to the driving pressure necessary to move air from the atmosphere to the alveoli. That pressure must overcome frictional losses secondary to resistance through the airways, and it must also expand the elastic element of the respiratory system above its resting volume. The relationship between this driving pressure and the forces it must overcome is described by the Equation of Motion of the Respiratory System, which portrays the lung as an elastic–resistive series model, like a balloon attached to a straw (Fig. 16.2). The equation states that the pressure required to move air into the alveoli is determined by the sum of the product of the desired volume change (i.e., tidal volume) and magnitude of how much the respiratory system (lungs and chest wall together) resists the resulting stretch (that is, the *Elastance* of the respiratory system), together with the product of the flow rate of air and resistance to flow through the airways. A third "pressure cost" relates to acceleration of gas molecules down the airway, but this pressure is trivial at normal respiratory rates and can be ignored under normal breathing conditions for simplicity. Thus, the simplified Equation of Motion for a spontaneously breathing person is written as follows:

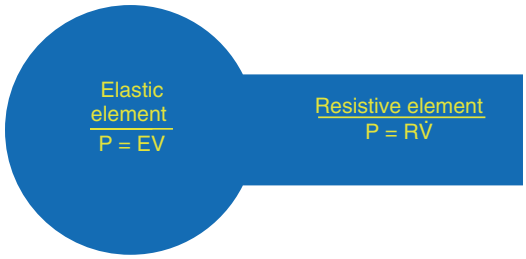

Fig. 16.2 The simplified Equation of Motion portrays the respiratory system in a series elastic model, akin to a balloon attached to a straw. The balloon represents the elastic component, while the straw is the resistive element. The pressure required to move air from the atmosphere into the alveoli is the sum of two products: the elastance (E) of the elastic component X the volume change (V) and airway resistance (R) X the flow of air through the airways ($\dot{V}$)

$$P_{mus} = EV + R\dot{V}$$

where P_{mus} is the pressure generated by the respiratory muscles, E is the elastance of the respiratory system, V is the desired volume change of the breath, R is the resistance through the respiratory system, and $\dot{V}$ is flow through the respiratory system. In other words, the equation states that there are two major loads in series, an elastic and a resistive one, that applied pressure must overcome to move air into the lungs.

In separating the different forces needed to inspire, the Equation of Motion also states that there must be a pressure difference down the airways in order to generate flow, and the pressure "cost" depends not only on how fast the air moves, but also on how much resistance in the respiratory system there is. Resistance describes frictional forces arising from both tissue movement and airflow through the airways. Frictional airway resistance occurs during breathing because of air molecules flowing through airways, and accounts for about 80% of total respiratory system resistance in adults [20]. Tissue resistance, which is usually a much smaller component of total respiratory system resistance, occurs because of displacement of tissues of the respiratory system during breathing.

When considering airway resistance, the relationship of individual airways to each other will influence the total airway resistance greatly. When airways are situated in parallel, as are small airways, individual resistances

down each airway are added reciprocally: $\frac{1}{R_{tot}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_n} \ldots$. Here, the resistance of all of the airways together is much smaller than the resistance of any single airway, so it would require an increase in resistance of many individual airways to increase the total resistance. In contrast, from the tip of the nose to the distal end of the trachea, resistances of intervening airway segments are arranged in series: that is, nasal, nasopharyngeal, oropharyngeal, hypopharyngeal, glottic, subglottic, and tracheal resistances are aligned one after the other. As such, those resistances are additive ($R_T = R_1 + R_2 + R_n \ldots$), so that each individual resistance is less than total resistance across that part of the airway. It also means that increasing the resistance in one part of that airway will directly increase total resistance (Fig. 16.3). Thus, increasing resistance in a proximal segment of the airway will require a greater total pressure drop to maintain flow, and so can exacerbate airway collapse in more distal segments. For example, an infant with moderate laryngomalacia can develop severe laryngeal obstructive symptoms when nasal congestion occurs because of the increase in nasal resistance: total respiratory system resistance increases, the intraluminal pressure drop across the nose will be greater, and simultaneously the infant will generate greater negative intrathoracic pressure to overcome that resistance. That combination will magnify the transmural pressure difference across the airway at the level of the supraglottis (as well as along all of the airway segments distal to the nose), favoring greater collapse of the supraglottic structures.

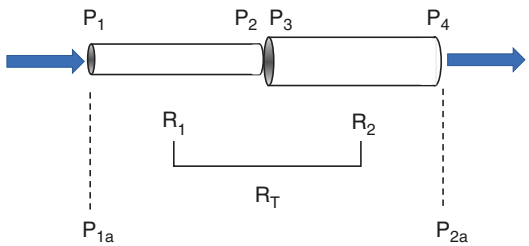

Fig. 16.3 In order for air to flow through an airway, pressure at the proximal end of the airway must be higher than pressure at the distal end. For a given flow rate, that pressure difference is determined by the resistance of the airway ($P1 - P2$ = Flow · Resistance). The larger airway in the diagram has a lower resistance across it than the smaller airway. If the two airways are placed in series, however, resistance across both airways will be greater than resistance through either one, so that the new proximal pressure (P_{1a}) will have to be higher than the proximal pressure through either of the individual airways (P_1 or P_3), and the pressure difference ($P_{1a} - P_{2a}$) has to be greater if flow is to remain constant

Airway Dynamics: Specific Considerations

The presence of airway narrowing that leads to stridor or wheezing often is state specific. When airway endoscopy is being considered, reproducing the conditions under which the noisy breathing occurs will increase the diagnostic yield and can make the difference between successfully determining the cause of the problem or not. For instance, adenotonsillar hypertrophy is considered to be the greatest risk factor for children to develop Obstructive Sleep Apnea (OSA) [21]. Nevertheless, an important mechanism for controlling patency of the pharynx is activation of the genioglossus muscle when intraluminal pressure becomes negative, but that reflex is lost or diminished in patients with obstructive sleep apnea [22]. Excessive sedation can result in collapse of the airway that might not be clinically relevant, but sedation titrated to effect can help identify the correct site of obstruction of the airway in patients with OSA [23]. At least 2 studies in children have shown that drug-induced sleep endoscopy has the potential to alter surgical approach based on findings of the studies [24, 25].

The state of the child during bronchoscopy is critical in interpreting findings of airway collapse. Airway caliber varies with respiratory cycle only slightly in a healthy infant breathing quietly, but the airway can narrow by as much as 50% if the infant cries or strains [26]. Similarly, small airway obstruction from bronchospasm or inflammation can produce cyclical intrathoracic

large airway dynamic collapse because the subject will increase pleural, and therefore transmural pressure to overcome the airway obstruction [26]. In adults, tracheobronchomalacia (TBM) is distinguished from this excessive dynamic airway collapse (EDAC) because TBM involves collapse of the cartilaginous portion of the airways, whereas EDAC refers to invagination of the pars membranacea (posterior membrane) while the cartilaginous rings maintain their shape [27]. Because the central airway is more compliant in infants than adults under normal circumstances, that differentiation may not be valid in infants and young children. These considerations are critical in the assessment of former preterm infants with severe bronchopulmonary dysplasia, who are at risk for central airway deformation and TBM because of exposure to positive pressure ventilation [28, 29], and who can also have severe small airway obstruction. Similarly, invagination of the posterior membrane during coughing is considered a normal finding during the maneuver [13, 30]. Excessive stimulation of the airway wall or inadequate topical anesthesia of the airway therefore can produce cough-induced airway collapse that could be misconstrued as abnormal.

Some conditions, like exercise-induced laryngeal obstruction, require replication of the stimuli that cause symptoms to yield the best chance of identifying a dynamic airway lesion [31, 32]. The larynx normally opens widely during exercise to increase flow across it while reducing resistance, but in some subjects, the larynx paradoxically narrows. Under resting conditions, there is usually no indication of an abnormality, and so ideally, laryngoscopy is performed under the same conditions that evince symptoms. Because there may also be a psychological component to laryngeal obstruction during exercise, a careful history must include all of the facts associated with exercise-induced dyspnea. One report, for instance, detailed a competitive swimmer who could cycle or run without difficulty, but upon entering a pool he would become dyspneic almost immediately [33]. Laryngoscopy during volitional hyperventilation was normal. When the patient was asked to hyperventilate while smelling chlorinated bleach, however, which simulated the odor of swimming in a chlorinated pool, he demonstrated paradoxical motion of the vocal cords almost immediately.

History

Certainly, all children who present with noisy breathing, chronic cough, or recurrent wheezing do not require bronchoscopic assessment. Some aspects of the history, however, can narrow the possible causes of a particular complaint, and contribute to the decision about the necessity for bronchoscopy. One group has created a mnemonic, SPECS-R, to determine the need for bronchoscopy in patients presenting with stridor (Table 16.1) [34]. Determining the cause of noisy breathing or wheezing from parental description of the sound is notoriously inaccurate [35–37], and physicians not specifically trained in airway disorders may also have difficulty characterizing the type of sound produced [38]. There are, however, other aspects of the history that can narrow the possible etiologies (Table 16.2). Broadly, the history designed to determine the cause of the problem includes timing, persistence, triggers, and predisposing factors for the problem. In addition to that information, details that would favor bronchoscopic evaluation include coexisting apnea, cyanosis, poor growth, and difficulty feeding [39].

Timing: Timing of symptoms includes age at which the problem began, whether the onset was abrupt or gradual, and whether the problem is

Table 16.1 Mnemonic for assessment of stridor [34]

S	*Severity* of airway obstruction according to parents' subjective impression
P	*Progression* of the obstruction
E	*Eating* or feeding difficulties, aspiration, failure to thrive
C	*Cyanotic* episodes, apneas, apparent life-threatening events
S	*Sleep* – obstruction so severe that sleep is disturbed
R	*Radiology* – specific abnormalities detected by radiographs

Table 16.2 Historical "2 Ts and 2 Ps"

Timing	Age at onset Abrupt or gradual
Triggers	Infectious or environmental factors Activities Sleep, eating, exercise
Persistence	Acute Chronic Intermittent Recurrent
Predisposing factors	Birth and obstetrical history Underlying conditions Prior surgeries

acute or chronic. Complaints that begin at or shortly after birth raise a concern for a congenital lesion of the airway [40]. Symptoms of congenital laryngomalacia, for instance, appear soon after birth. They worsen between 4 and 8 months, improve by 12 months, and typically resolve by 12–18 months [41]. Similarly, as many as 90% of airway hemangiomata present by 6 months of age [40, 42]. An infant who wheezes soon after birth is unlikely to have asthma but is more likely to have a lesion that causes airway narrowing from extrinsic compression, intraluminal obstruction, or abnormal airway collapsibility. Wheezing in an otherwise healthy toddler that develops abruptly and is accompanied by respiratory distress without a viral prodrome should raise concern for a retained foreign body. Some central airway lesions can be present but provide only subtle findings until the child acquires an acute respiratory illness, after which they become more clinically apparent. Inducible laryngeal obstruction, often referred to as Vocal Cord Dysfunction, does not typically occur in children younger than school age [43].

Persistence: Symptoms can be acute, chronic, persistent, intermittent, or recurrent. Lesions that cause intermittent symptoms probably result from dynamic airway narrowing rather than structural abnormalities. The intermittent nature of symptoms also can reflect severity of airway compromise. For instance, with minor degrees of airway narrowing, there may be no noisy breathing at rest, but, with increased effort, stridor can develop [39]. Recurrent problems can occur with viral illnesses or upon repeated exposure to an appropriate trigger but be absent during periods of wellness. The character of the persistence of symptoms often influences the need for or timing of bronchoscopy: since persistent chronic symptoms typically reflect a greater degree of airway narrowing, bronchoscopic evaluation is more likely to be considered.

Triggers: The most common trigger for infants and young children with recurrent wheezing is viral respiratory infection [44]. Viral upper respiratory infections can also exacerbate stridor or noisy breathing from any etiology because of the effect of mucosal edema and increased secretions on resistance throughout the extrathoracic airway. Similarly, infants with tracheobronchomalacia will have greater symptoms when any potential trigger results in an increase in expiratory effort, like crying or straining to pass a stool. Infants and toddlers who cough primarily during the act of drinking or eating, rather than after a meal, are at risk for swallowing dysfunction or a laryngeal cleft, or less commonly an H-type tracheoesophageal fistula. Exercise and emotional stress can be a trigger for inducible laryngeal obstruction, and the timing and duration of noisy breathing and associated dyspnea are distinct from those of exercise-induced bronchospasm [45].

Predisposing Factors: For children with noisy breathing, the search for predisposing factors often begins at birth. Clues to the etiology include information about the method of delivery and whether excessive traction on the neck was required. Presence of a shoulder dystocia would support this, although its absence would not preclude injury to the recurrent laryngeal nerve. Need for airway instrumentation and presence and duration of airway intubation would raise the concern for acquired glottic and subglottic lesions. A maternal history of perineal condylomata could help explain dysphonia or abnormal chest findings related to airway papillomas. Beyond a birth history, a history of prior neck or thoracic surgeries could point toward causes of stridor. Other known conditions that are associated with airway lesions, like Chiari

malformation (vocal cord paralysis), tracheoesophageal fistula with esophageal atresia (intrathoracic tracheomalacia), ventricular septal defect with large left to right shunt (left vocal cord paralysis and/or left main or lower lobe bronchus compression), all increase the risk of abnormal findings on bronchoscopy if the patient has stridor or wheezing.

Physical Examination

The physical findings that must be considered are directed toward the quality and characteristics of the abnormal sound, any associated changes to voice, clinical features that could predispose toward the problem, and the impact of the problem on the patient's breathing effort and overall growth and development. Together, these factors address the etiology and location of the problem as well as its impact on gas exchange.

In children with noisy breathing or recurrent wheezing, the type of noise that is generated reflects the site of obstruction (Table 16.3). With careful attention, the character of the noise can give important clues to the cause of noisy breathing or wheezing. Stridor reflects obstruction that is typically extrathoracic, and so it is usually an inspiratory sound because of the accentuated airway narrowing that occurs on inspiration in the extrathoracic airway. It can be bi-phasic when it is caused by a fixed lesion-like subglottic stenosis, when airway caliber does not vary with the phase of respiration. Stridor can be of varying pitch: some authors divide stridor into "voiced," describing a sound comprised of pure tones and overtones, and "fricative," referring to a noise-like sound [39]. Fricative stridor can be confused with stertor, a low-pitched, wet noise akin to snoring. Stertor is typically caused by obstructing lesions of the nasopharynx, oropharynx, and hypopharynx [34], although the quality of sound from those lesions has also been described as fricative stridor [39]. Pharyngeal-derived stertor occasionally can be biphasic. High-pitched, voiced stridor typically reflects lesions in the glottis or supraglottis, although laryngomalacia can also cause a low-pitched and fluttering stridor [34]. Longitudinal traction of the extrathoracic airway associated with neck extension will stiffen the airway to some degree, and so can make stridor related to extrathoracic tracheomalacia and laryngomalacia better. Conversely, neck flexion will exacerbate the stridor from those causes. A jaw thrust will ameliorate stridor or stertor related to glossoptosis and perhaps that due to hypopharyngeal hypotonia or pharyngomalacia. Similarly, prone positioning can improve the airway obstruction related to these problems as well as to laryngomalacia [46].

Wheezing is a musical sound that reflects intrathoracic airway obstruction. It occurs more commonly during exhalation because of the tendency for intrathoracic airways to narrow during that phase of breathing. It is caused by turbulent airflow through a narrowed airway; thus, there must be adequate flow to hear wheezes. Even when obstruction occurs primarily in small airways, there must be narrowing of medium-sized airways in order for wheezes to be generated. This can be the result of the same process that caused the small airway obstruction (bronchospasm, airway wall edema, secretions) or from dynamic compression resulting from increased pleural pressure generated to overcome the obstruction of the small airways. Infants and children with small airway obstruction often will breathe with a rapid and shallow breathing pattern, and wheezing can be overlooked unless the child is asked to breathe deeply and exhale forcefully. In subjects too young to follow such directions, the examiner can exert pressure on

Table 16.3 Noises, voice, and site of obstruction

Noise	Site
Snoring, gurgling	Pharynx, hypopharynx
High pitched	Supraglottic, glottic
Homophonous wheeze	Intrathoracic central airways
Heterophonous wheeze	Peripheral airways
Voice/cry	**Nasopharynx**
Hyponasal	Supraglottic
Muffled	Glottic
Hoarse/aphonia	Subglottic
Weak/soft	Intrathoracic
Normal	

the chest wall in the anterior–posterior direction in synchrony with an expiratory effort ("squeeze the wheeze"). When airway obstruction is caused by disease processes that affect small- and medium-sized airways, there are regional differences in the degree of airway narrowing. As a result, different sets of notes are generated in different regions of the chest. Thus, these "polyphonic" or "heterophonous" wheezes reflect wheezing that results from small or peripheral airway obstruction. In contrast, when obstruction occurs from a lesion in a central airway, the set of notes generated by that single obstruction will be the same throughout the chest, although their amplitude can vary depending on the distance away from the obstruction the observer listens. This type of wheezing is called "monophonic" or "homophonous" and reflects a large airway lesion like an endobronchial mass, airway compression, or tracheo- or bronchomalacia. Some authors refer to this type of wheezing as expiratory stridor, but that is a confusing term, which should be avoided. Every effort should be made by the examiner to determine whether wheezes are polyphonic/heterophonous or monophonic/homophonous, as the latter are much more frequently associated with lesions that should be evaluated bronchoscopically.

In addition to the character of the noise under investigation, alterations in voice can give important clues as to the level of obstruction. Hyponasal speech is associated with nasopharyngeal obstruction, like adenoidal hypertrophy. A muffled or "hot potato" voice reflects supraglottic obstruction like tonsillar hypertrophy or a supraglottic cyst. In contrast, patients with glottic obstruction like a glottic web or vocal cord paralysis can produce a hoarse voice or be aphonic. Children with subglottic lesions like subglottic stenosis will have a weak voice or a soft cry. Those children with intrathoracic lesions typically will have a normal voice.

Beyond findings related to the respiratory complaint under investigation, there may be other physical clues to the diagnosis or findings that predispose the patient to the respiratory difficulty under investigation (Table 16.4). Patients who present with stridor should have a careful examination of craniofacial structures that include patency of the nasal passages, assessment of the midface for malar flattening or "adenoidal facies," visualization of the oropharynx to rule out tonsillar hypertrophy, macroglossia, or a crowded oropharyngeal vault, and an assessment of the mandible to rule out micrognathia or retrognathia that could predispose to glossoptosis and upper airway obstruction. The examiner should perform a general evaluation for findings consistent with syndromes that are associated with airway obstruction. The skin should be examined for hemangiomata, as 50% of children with an airway hemangioma have a cutaneous lesion as well [47]. The association may be even stronger if the cutaneous hemangioma occurs in a "beard" distribution that includes the preauricular areas, lower lip, chin, and anterior neck [48]. The evaluation should also include an assessment of the child's resting tone, as infants with pharyngomalacia also often have generalized hypotonia and delayed motor development [34]. In children with chronic cough or recurrent wheezing, the presence of digital clubbing raises concern for a pyogenic process in the chest like bronchiectasis, and diseases like cystic fibrosis or primary ciliary dyskinesia should be considered.

Table 16.4 Physical examination: general considerations

Type of noise	Stridor, stertor, homophonous/monophonic wheeze, heterophonous/polyphonic wheeze
Phase of respiration	Inspiratory, expiratory, biphasic
Other findings	Craniofacial problems, syndromes, cutaneous hemangiomata, digital clubbing
Degree of distress	Retractions, accessory muscle use

Finally, there are physical findings that reflect the severity of obstruction and the impact of the respiratory problem on the overall status of the child. Intercostal, suprasternal, supraclavicular, and sternal retractions reflect a need for the child to generate increased negative intrathoracic pressure to achieve inspiration. This can be the result of decreased lung compliance or increased resistance anywhere along the airways, so that their presence alone does not distinguish between intrathoracic and extrathoracic disease. For

example, those retractions could be present in an infant with severe laryngomalacia or a child with bronchiolitis. Their presence and severity directly mirror the child's breathing effort and degree of respiratory distress. Subcostal retractions, however, reflect caudal displacement or flattening of the diaphragm because of hyperinflation, and their presence is associated with intrathoracic airway obstruction. Nasal flaring and head bobbing are signs of inspiratory accessory muscle use and they also reflect the child's degree of respiratory distress. Abdominal expiratory accessory muscle use signifies more severe intrathoracic airway obstruction; occasionally, it is accompanied by expiratory bulging of the intercostal or suprasternal spaces, reflecting the high pleural pressures being generated to overcome the obstruction and facilitate exhalation. If chronic airway obstruction is severe enough, the child may not be able to eat adequately. Additionally, use of accessory muscles increases the amount of work required by the muscles of respiration and the metabolic cost of breathing. The combination of decreased caloric intake and increased metabolic expenditure can lead to growth failure. When airway obstruction is severe enough to disrupt sleep and interfere with nourishment, it can also cause developmental delay. While these findings do not necessarily provide insight into the cause of a child's noisy breathing, wheezing, or chronic cough, they do reflect the severity of the problem and so contribute to the decision for and timing of airway endoscopy.

Conclusion

Airway endoscopy has become a powerful tool in the armamentarium of healthcare providers who care for infants and children with respiratory disorders. Nevertheless, it should be used selectively to minimize risks and cost of care. A careful history and physical examination can help the practitioner identify those problems that would be most amenable to bronchoscopic examination. Furthermore, understanding the conditions under which the respiratory abnormality occurs in a given patient can allow the endoscopist to reproduce or closely simulate similar conditions during the airway evaluation to enhance the diagnostic yield of the procedure. Importantly, an understanding of the physiology of dynamic airway mechanics during tidal breathing, forced exhalation, and cough can help the endoscopist distinguish between normal and abnormal phenomena.

References

1. Faro A, Wood RE, Schechter MS, Leong AB, Wittkugel E, Abode K, et al. Official American Thoracic Society technical standards: flexible airway endoscopy in children. Am J Respir Crit Care Med. 2015;191(9):1066–80.
2. Midulla F, de Blic J, Barbato A, Bush A, Eber E, Kotecha S, et al. Flexible endoscopy of paediatric airways. Eur Respir J. 2003;22(4):698–708.
3. Boesch RP, Baughn JM, Cofer SA, Balakrishnan K. Trans-nasal flexible bronchoscopy in wheezing children: diagnostic yield, impact on therapy, and prevalence of laryngeal cleft. Pediatr Pulmonol. 2018;53(3):310–5.
4. Godfrey S, Avital A, Maayan C, Rotschild M, Springer C. Yield from flexible bronchoscopy in children. Pediatr Pulmonol. 1997;23(4):261–9.
5. Nussbaum E. Pediatric fiberoptic bronchoscopy: clinical experience with 2,836 bronchoscopies. Pediatr Crit Care Med. 2002;3(2):171–6.
6. Schellhase DE, Fawcett DD, Schutze GE, Lensing SY, Tryka AF. Clinical utility of flexible bronchoscopy and bronchoalveolar lavage in young children with recurrent wheezing. J Pediatr. 1998;132(2):312–8.
7. Wood RE. The diagnostic effectiveness of the flexible bronchoscope in children. Pediatr Pulmonol. 1985;1(4):188–92.
8. Wood RE. Evaluation of the upper airway in children. Curr Opin Pediatr. 2008;20(3):266–71.
9. Eastwood PR, Platt PR, Shepherd K, Maddison K, Hillman DR. Collapsibility of the upper airway at different concentrations of propofol anesthesia. Anesthesiology. 2005;103(3):470–7.
10. Litman RS, McDonough JM, Marcus CL, Schwartz AR, Ward DS. Upper airway collapsibility in anesthetized children. Anesth Analg. 2006;102(3):750–4.
11. Nielson DW, Ku PL, Egger M. Topical lidocaine exaggerates laryngomalacia during flexible bronchoscopy. Am J Respir Crit Care Med. 2000;161(1):147–51.
12. Hysinger EB, Panitch HB. Paediatric Tracheomalacia. Paediatr Respir Rev. 2016;17:9–15.
13. Knudson RJ, Mead J, Knudson DE. Contribution of airway collapse to supramaximal expiratory flows. J Appl Physiol. 1974;36(6):653–67.
14. Croteau JR, Cook CD. Volume-pressure and length-tension measurements in human tracheal and bronchial segments. J Appl Physiol. 1961;16:170–2.
15. Penn RB, Wolfson MR, Shaffer TH. Developmental differences in tracheal cartilage mechanics. Pediatr Res. 1989;26(5):429–33.

16. Panitch HB, Allen JL, Ryan JP, Wolfson MR, Shaffer TH. A comparison of preterm and adult airway smooth muscle mechanics. J Appl Physiol (1985). 1989;66(4):1760–5.
17. Bhutani VK, Koslo RJ, Shaffer TH. The effect of tracheal smooth muscle tone on neonatal airway collapsibility. Pediatr Res. 1986;20(6):492–5.
18. Palombini B, Coburn RF. Control of the compressibility of the canine trachea. Respir Physiol. 1972;15(3):365–83.
19. Panitch HB, Keklikian EN, Motley RA, Wolfson MR, Schidlow DV. Effect of altering smooth muscle tone on maximal expiratory flows in patients with tracheomalacia. Pediatr Pulmonol. 1990;9(3):170–6.
20. Marshall R, Dubois AB. The measurement of the viscous resistance of the lung tissues in normal man. Clin Sci. 1956;15(1):161–70.
21. Gulotta G, Iannella G, Vicini C, Polimeni A, Greco A, de Vincentiis M, et al. Risk factors for obstructive sleep apnea syndrome in children: state of the art. Int J Environ Res Public Health. 2019;16(18):3235.
22. Wheatley JR, Mezzanotte WS, Tangel DJ, White DP. Influence of sleep on genioglossus muscle activation by negative pressure in normal men. Am Rev Respir Dis. 1993;148(3):597–605.
23. Albdah AA, Alkusayer MM, Al-Kadi M, Almofada H, Alnofal EA, Almutairi S. The impact of drug-induced sleep endoscopy on therapeutic decisions in obstructive sleep apnea: a systematic review and meta-analysis. Cureus. 2019;11(10):e6041.
24. Collu MA, Esteller E, Lipari F, Haspert R, Mulas D, Diaz MA, et al. A case-control study of drug-induced sleep endoscopy (DISE) in pediatric population: a proposal for indications. Int J Pediatr Otorhinolaryngol. 2018;108:113–9.
25. Gazzaz MJ, Isaac A, Anderson S, Alsufyani N, Alrajhi Y, El-Hakim H. Does drug-induced sleep endoscopy change the surgical decision in surgically naive non-syndromic children with snoring/sleep disordered breathing from the standard adenotonsillectomy? A retrospective cohort study. J Otolaryngol Head Neck Surg. 2017;46(1):12.
26. Wittenborg MH, Gyepes MT, Crocker D. Tracheal dynamics in infants with respiratory distress, stridor, and collapsing trachea. Radiology. 1967;88(4):653–62.
27. Murgu S, Colt H. Tracheobronchomalacia and excessive dynamic airway collapse. Clin Chest Med. 2013;34(3):527–55.
28. Bhutani VK, Rubenstein D, Shaffer TH. Pressure-induced deformation in immature airways. Pediatr Res. 1981;15(5):829–32.
29. Sotomayor JL, Godinez RI, Borden S, Wilmott RW. Large-airway collapse due to acquired tracheobronchomalacia in infancy. Am J Dis Child. 1986;140(4):367–71.
30. Ross BB, Gramiak R, Rahn H. Physical dynamics of the cough mechanism. J Appl Physiol. 1955;8(3):264–8.
31. Olin JT, Clary MS, Deardorff EH, Johnston K, Morris MJ, Sokoya M, et al. Inducible laryngeal obstruction during exercise: moving beyond vocal cords with new insights. Phys Sportsmed. 2015;43(1):13–21.
32. Roksund OD, Maat RC, Heimdal JH, Olofsson J, Skadberg BT, Halvorsen T. Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways. Respir Med. 2009;103(12):1911–8.
33. Bhargava S, Panitch HB, Allen JL. Chlorine induced paradoxical vocal cord dysfunction. Chest. 2000;118(4 (Suppl)):295S (Abstract).
34. Zoumalan R, Maddalozzo J, Holinger LD. Etiology of stridor in infants. Ann Otol Rhinol Laryngol. 2007;116(5):329–34.
35. Elphick HE, Sherlock P, Foxall G, Simpson EJ, Shiell NA, Primhak RA, et al. Survey of respiratory sounds in infants. Arch Dis Child. 2001;84(1):35–9.
36. Saglani S, McKenzie SA, Bush A, Payne DN. A video questionnaire identifies upper airway abnormalities in preschool children with reported wheeze. Arch Dis Child. 2005;90(9):961–4.
37. Shanmugam S, Nathan AM, Zaki R, Tan KE, Eg KP, Thavagnanam S, et al. Parents are poor at labelling wheeze in children: a cross-sectional study. BMC Pediatr. 2016;16:80.
38. Naseri I, Durden FL, Sobol SE. Pediatric airway consultation survey in a tertiary care children's hospital: an interobserver analysis. Ear Nose Throat J. 2009;88(12):1266–8.
39. Pfleger A, Eber E. Assessment and causes of stridor. Paediatr Respir Rev. 2016;18:64–72.
40. Bluher AE, Darrow DH. Stridor in the Newborn. Pediatr Clin N Am. 2019;66(2):475–88.
41. Thompson DM. Laryngomalacia: factors that influence disease severity and outcomes of management. Curr Opin Otolaryngol Head Neck Surg. 2010;18(6):564–70.
42. Cotton RT, Richardson MA. Congenital laryngeal anomalies. Otolaryngol Clin N Am. 1981;14(1):203–18.
43. Hicks M, Brugman SM, Katial R. Vocal cord dysfunction/paradoxical vocal fold motion. Prim Care. 2008;35(1):81–103, vii.
44. Jartti T, Gern JE. Role of viral infections in the development and exacerbation of asthma in children. J Allergy Clin Immunol. 2017;140(4):895–906.
45. Tilles SA. Exercise-induced respiratory symptoms: an epidemic among adolescents. Ann Allergy Asthma Immunol. 2010;104(5):361–7; quiz 8-70, 412.
46. Ayari S, Aubertin G, Girschig H, Van Den Abbeele T, Mondain M. Pathophysiology and diagnostic approach to laryngomalacia in infants. Eur Ann Otorhinolaryngol Head Neck Dis. 2012;129(5):257–63.
47. Pryor MP. Noisy breathing in children: history and presentation hold many clues to the cause. Postgrad Med. 1997;101(2):103–12.
48. O-Lee TJ, Messner A. Subglottic hemangioma. Otolaryngol Clin N Am. 2008;41(5):903–11, viii-ix.

Evaluating Airway Dynamics

17

Erik B. Hysinger

Evaluation of Upper Airway Dynamics

Nasopharyngolaryngoscopy (NPL)

Approximately 30% of children will have noisy breathing prior to 6 months of age [1]. Although intermittent noisy breathing is typically benign and self-resolving, persistent noisy breathing can suggest upper airway pathology. Flexible nasopharyngolaryngoscopy (NPL) is commonly performed in awake children and allows assessment of airway dynamics to the level of the glottis in the office setting. Because of the favorable safety profile and lack of sedation, NPL is often the first step in the evaluation of airway dynamics in children [2].

Laryngomalacia is the most common dynamic abnormality of the pediatric airway and accounts for more than 60% of the cases of stridor in young children. Laryngomalacia is characterized by the collapse of supraglottic structures and airflow obstruction during inspiration; NPL is the gold standard for diagnosing laryngomalacia (Fig. 17.1). While the diagnosis of laryngomalacia is best made by direct visualization, laryngomalacia will resolve without intervention in a majority of cases [3]. Consequently, the need for surgical intervention should be based on severe clinical symptoms such as respiratory distress, failure to thrive, and obstructive sleep apnea rather than the severity of findings on endoscopy [4].

NPL is particularly critical for assessment of vocal cord motion. In children, general anesthesia can result in normal, absent, unilateral, or paradoxical motion of the vocal cords; however, this problem is avoided in an awake patient [5]. Unfortunately, NPL is limited by the inability to assess structures beyond the vocal cords or dynamic airway pathology related to airway obstruction during sleep.

Drug-Induced Sleep Endoscopy (DISE)

Obstructive sleep apnea (OSA) affects more than 5% of children and is a common indication for evaluating upper airway dynamics [6]. More than 40% of patients with OSA that undergo adenotonsillectomy have residual disease or develop recurrent OSA [7]. For patients who do not respond adequately to adenotonsillectomy, DISE allows for a complete assessment of upper airway dynamics including the nasopharynx, palate, pharyngeal wall, tongue base, and supraglottis. Findings based on DISE can be used to guide both surgical and nonsurgical management of OSA. While there is not a universally

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_17

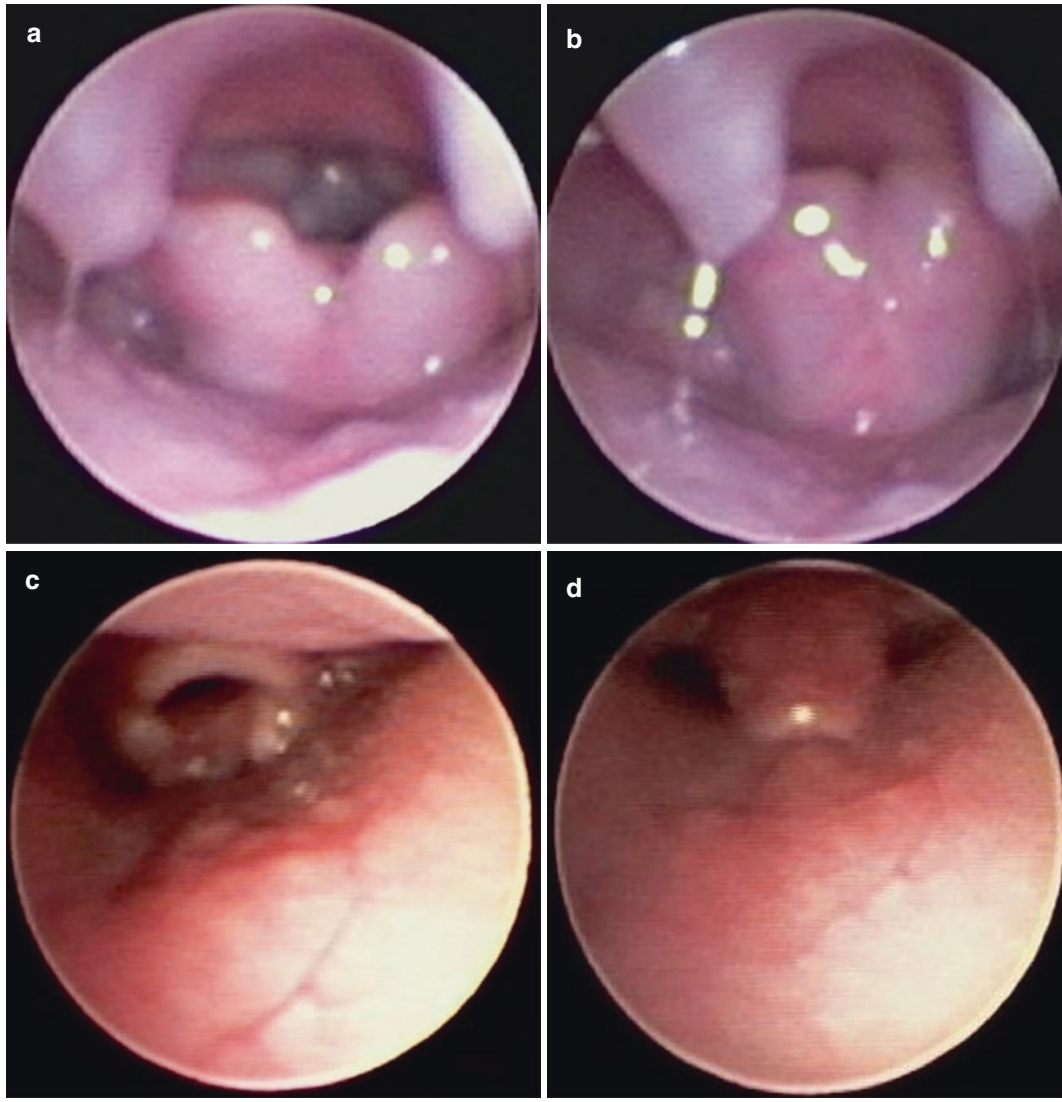

Fig. 17.1 Endoscopic images from an NPL of the larynx during exhalation (**a**) and inspiration (**b**) for a patient with laryngomalacia characterized arytenoids prolapse and during exhalation (**c**) and inspiration (**d**) for a patient with laryngomalacia characterized by collapse of the epiglottis

accepted sedation approach to DISE, it is clear that different anesthetics can alter upper airway dynamics [8].

Topical anesthesia with lidocaine is frequently utilized in the assessment of the upper airway. The application of topical lidocaine can reduce airway reflexes and worsen laryngomalacia scoring in adults [9, 10]; however, other reports have found limited impact on airway lumen patency [11]. Similarly, the impact of lidocaine on the apnea hypopnea index based on polysomnography has shown mixed results [12, 13]. Most patients undergoing DISE are able to tolerate endoscopy without topical anesthetic; consequently, agents such as lidocaine are often not needed until evaluating the lower airway. However, general anesthesia can alter upper airway dynamics.

Propofol is often used for anesthesia during sleep-state endoscopy. In children, propofol

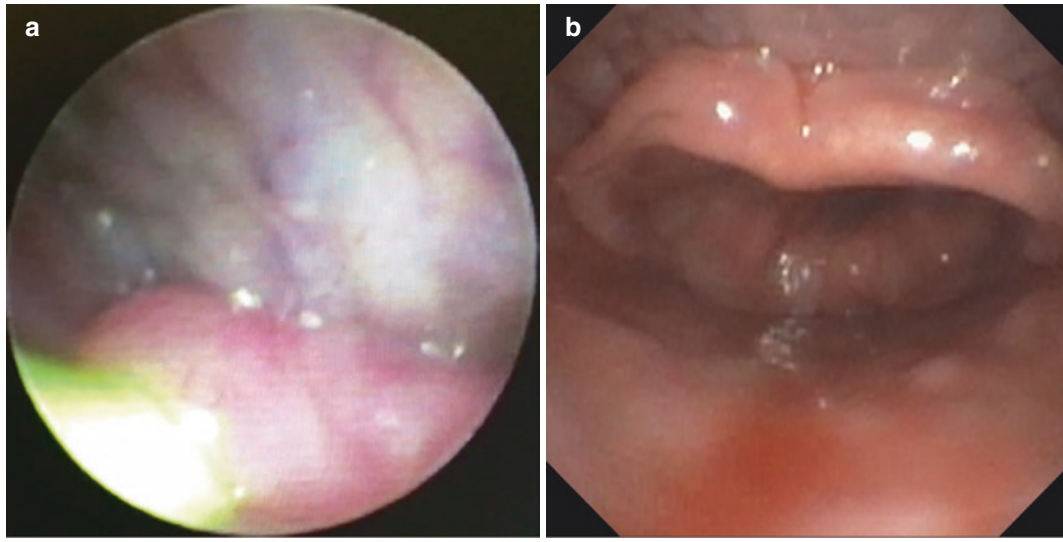

Fig. 17.2 Endoscopic images from an NPL for a patient with mucopolysaccharidosis II and severe upper airway obstruction. The tongue base and epiglottis are completely collapsed in the anterior–posterior plane under deep sedation with propofol and sevoflurane (**a**) and only partially collapsed under light sedation with propofol and sevoflurane (**b**). The nasogastric tube (yellow) has been remove in panel (**b**)

results in a dose-dependent reduction in the caliber of the airway. The change in airway dynamics can be seen throughout the airway in infants, and is most prominent at the epiglottis and tongue base (Fig. 17.2) [14–16]. Similarly, inhaled anesthetics such as sevoflurane, isoflurane, and halothane alter airway muscle tone and cross-sectional area in a dose-dependent manner. Unlike with propofol, the soft palate appears to be the most commonly affected structure by inhaled anesthetics [17, 18]. Opiates and benzodiazepines can also increase upper airway obstruction; however, the dose response is less clear [19, 20].

Dexmedetomidine (DEX) has more recently been used in the assessment of upper airway dynamics. Although some reports have shown no differences in upper airway morphology in patients anesthetized with DEX compared to propofol at low dose [21], increasing depth of sedation with DEX has minimal impact on the extent of airway collapse unlike other agents [22, 23]. Given the minimal impact on airway tone, DEX could be an ideal anesthetic agent for DISE.

While it is clear that anesthetic agents can alter airway tone, procedural technique also impacts assessment of the upper airway. Currently, there are multiple scoring systems, typically based on local clinical practice, for DISE. There is no consensus on which method correlates best with patient outcomes and only limited data in children. The VOTE (velum, oropharynx, tongue base, and epiglottis) classification system is the most commonly used and relies on a qualitative assessment of airway narrowing [24, 25]. However, interrater assessment of upper airway narrowing can be quite variable during DISE, particularly with regard to severity of dynamic abnormalities [26–28]. Upper airway collapse can also be altered by the position of the patient, supine versus side-lying [29], and rotation of the head and neck [30]. Unfortunately, patient positioning is not systematically accounted for in existing scoring systems for DISE. Despite the lack of standardization, DISE can guide decision-making and predict surgical outcomes in the management of upper airway obstruction [28, 31].

Cine MRI

Cine MRI provides and alternative, non-endoscopic method to evaluate upper airway dynamics and is particularly useful in patients with residual OSA following adenotonsillectomy

[32, 33]. Typically, cine MRI is performed in a sleep-state with either propofol or DEX. Cine MRI correlates well with DISE and permits evaluation of multiple level of airway obstruction simultaneously [34].

Evaluation of Lower Airway Dynamics

Flexible Bronchoscopy

Dynamic lower airway pathologies such as tracheomalacia are the most common abnormalities of the pediatric trachea and affect approximately 1:2100 otherwise healthy children. The prevalence of dynamic pathologies is much more common in patients with other comorbidities such as tracheoesophageal fistulas, congenital heart disease, and bronchopulmonary dysplasia [35–37]. There are increasingly pharmacologic and surgical treatments that may be useful for the treatment of dynamic lower airway pathologies such as cholinergic agents, endobronchial stents, aortopexy, and tracheopexy [38–42]. However, there is no current validated, standardized approach to the assessment of lower airway dynamics in children to determine which patients would benefit from intervention or which intervention is most effective.

The trachea and bronchi are dynamic structures that change both size and shape during the respiratory cycle. The presence and extent of dynamic lower airway collapse depends both on intrinsic properties of the airway wall and the transmural airway pressure (P_{TM}) [43–45], where the P_{TM} is the difference of the airway lumen pressure (P_{LUM}) and pleural pressure (P_{Pl}):

$$P_{TM} = P_{Lum} - P_{Pl}.$$

As P_{TM} increases, there is more collapsing force exerted on the airway and a reduction in the airway cross-sectional area. Dynamic airway pathologies are most appropriately thought of as abnormalities of tracheal compliance with excessive airway collapse for a given P_{TM}. While there are in vivo methods to evaluate P_{TM}, this is not routinely done during bronchoscopy.

As with assessment of upper airway dynamics, anesthesia plays a critical role when evaluating lower airway dynamics. Unfortunately, there is no standardized anesthetic approach for performing bronchoscopy. Similarly, the impact of different anesthetic agents on the endoscopic assessment of the lower airway is entirely unknown. Regardless of the impact of different anesthetic agents on airway dynamics, depth of sedation impacts motion of the airway.

Lower airway dynamics are typically assessed during quiet, spontaneous respiration. If a patient is over-sedated and making minimal or no spontaneous effort, the P_{TM} will be decreased, potentially masking dynamic pathology. Conversely, if a patient is under-sedated and coughing or performs a Valsalva maneuver due to agitation, P_{TM} increases and exerts a greater collapsing force on the airway (Fig. 17.3). In patients that are only symptomatic with coughing, it can be useful to provoke coughing during bronchoscopy.

Endoscopic technique can also have a significant impact on respiratory mechanics and alter lower airway dynamics. In general, it is preferable to utilize the smallest flexible bronchoscope possible when performing a dynamic assessment of the lower airway. The bronchoscope should be inserted via a transnasal approach with the patient spontaneously breathing. The presence of the bronchoscope itself creates partial occlusion of the airway when passed through the glottis, which increases airway resistance and reduces tidal volume [46]. Although this is minimized if the airway is large relative to the size of the bronchoscope, changes in respiratory mechanics can be quite pronounced [47].

While assessment of lower airway dynamics is best done via a transnasal approach, dynamic assessment can be important in patients with chronic respiratory failure who require invasive positive pressure ventilation. The artificial airway can bypass abnormal segments of the airway, making it impossible to visualize airway dynamics. By withdrawing the endotracheal or tracheostomy tube under direct visualization with the bronchoscope, these areas can be assessed. In all but the most severe cases, positive pressure can temporarily be held to evaluate the airway in the

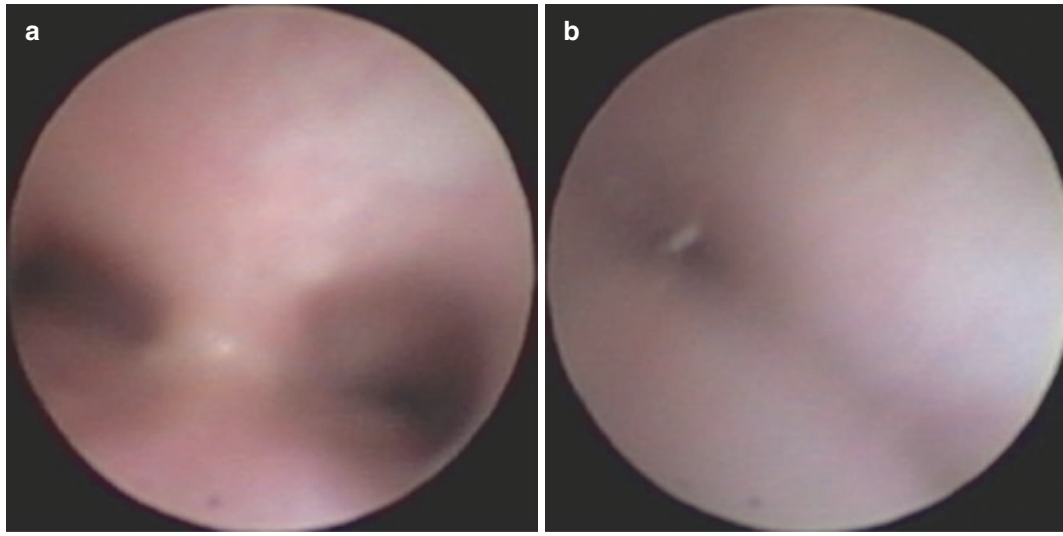

Fig. 17.3 Endoscopic images of a patent distal trachea during quiet breathing (**a**) and near complete collapse during a Valsalva maneuver (**b**)

most natural state possible. The flexible bronchoscope can occlude a large fraction of an artificial airway and generate auto-PEEP [47]. PEEP increases pressure within the airway lumen and can improve respiratory mechanics, masking the presence of dynamic lower airway pathologies [48, 49]. Thus, lower airway dynamics must be interpreted with caution if performed via an artificial airway.

When evaluating lower airway dynamics, the visual appearance of dynamic causes of airway obstruction such as tracheomalacia can be quite similar to fixed causes of obstruction such as vascular compression. Potential treatment options are often different as well, so it is important to distinguish dynamic from fixed lower airway obstruction. Although the use of an artificial airway and PEEP should be avoided for the initial assessment of lower airway dynamics when possible, application of PEEP can help distinguish dynamic pathology from fixed pathology. PEEP will increase the caliber of the airway lumen for dynamic airway obstruction (Fig. 17.4), but will have minimal impact on the appearance of fixed pathologies. This strategy may also be useful for optimizing ventilator support for patients with dynamic lower airway obstruction.

When assessing the extent of airway collapse based on flexible bronchoscopy, several factors regarding the optics of the bronchoscope should be taken into consideration. There is radial distortion of the image on the periphery of the field of view such that there is greater magnification as an object is further from the center of field of view. Further, magnification changes depending on the distance to the object and increases exponentially if the bronchoscope is within 0.5 cm. During spontaneous, quiet breathing diaphragmatic excursion can be up to 2 cm [50], which causes the airway to move away from the bronchoscope and can alter the assessment of the airway. Consequently, to optimally assess the airway dynamics, the relative position of the bronchoscope and the airway must remain constant.

Most experts agree that more than 50% collapse of the airway during spontaneous respiration is abnormal [51]; however, normative data are lacking, and the impact of changing airway compliance with age is not considered. Recent efforts have also focused on defining the severity of airway collapse [51], but the extent and location of airway collapse does not appear to correlate well with clinical symptoms and outcomes in children [52]. Ultimately, assessment of airway collapse based on bronchoscopy is subjective and

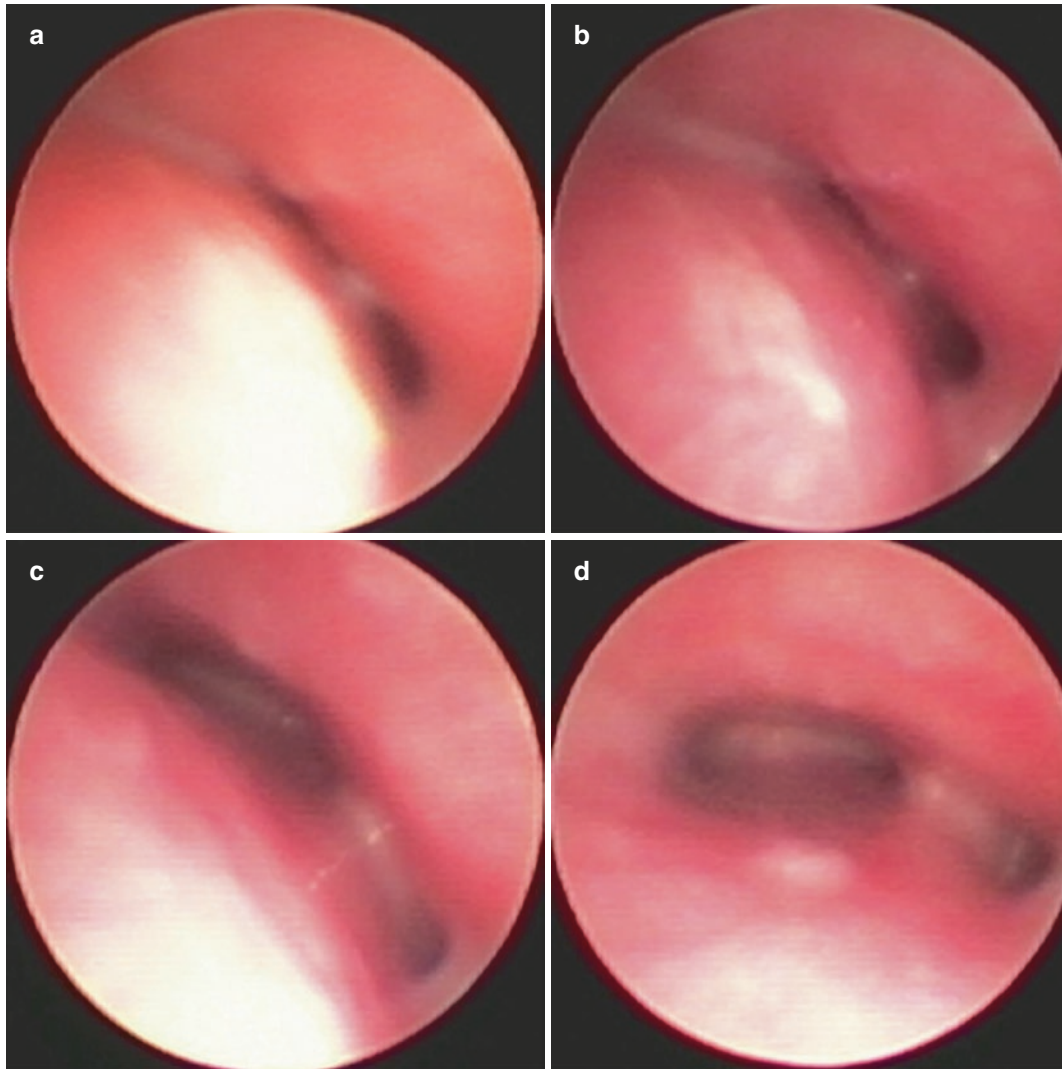

Fig. 17.4 Endoscopic views of the distal trachea of a patient with tracheomalacia. The bronchoscope has been passed through the tracheostomy tube and PEEP has been titrated to 5 (**a**), 10 (**b**), 15 (**c**), and 20 (**d**) cm H_2O with progressive expansion of the tracheal lumen

complicated by the optical limitations of the bronchoscope. Objective methods to quantify airway cross-sectional area have been developed but are seldom used in clinical practice [52, 53]. Fortunately, there is good inter-rater agreement for the qualitative assessment of lower airway dynamics in adults [54]. This needs to be evaluated formally in children.

Despite the challenges of assessing lower airway dynamics with flexible bronchoscopy, it is generally considered the "gold standard" for evaluation of lower airway dynamics. Performing flexible bronchoscopy under carefully regulated anesthesia in a natural airway without an endotracheal tube, tracheostomy tube, or laryngeal mask airway is critical to optimizing the understanding of lower airway motion.

Rigid Bronchoscopy

While flexible bronchoscopy is usually preferred when assessing lower airway dynamics, rigid bronchoscopy is often used, especially if flexible

bronchoscopy is not available. Rigid bronchoscopy relies on the use of a laryngoscope and either a rigid ventilating bronchoscope or Hopkins rod telescope, which can alter the airway, and often requires a deeper level of sedation; however, there are marked advantages of the optical resolution with rigid instrumentation [55]. There is limited evidence comparing flexible and rigid bronchoscopy for evaluating lower airway dynamics. Although the extent of airway collapse is typically well correlated, there can be significant difference between the two techniques, even when performed under the same sedation (Fig. 17.5) [56, 57].

Imaging

Multiple imaging modalities have been utilized to evaluate dynamics of the lower airway and can provide additional information to obtain a more comprehensive understanding of the airway motion.

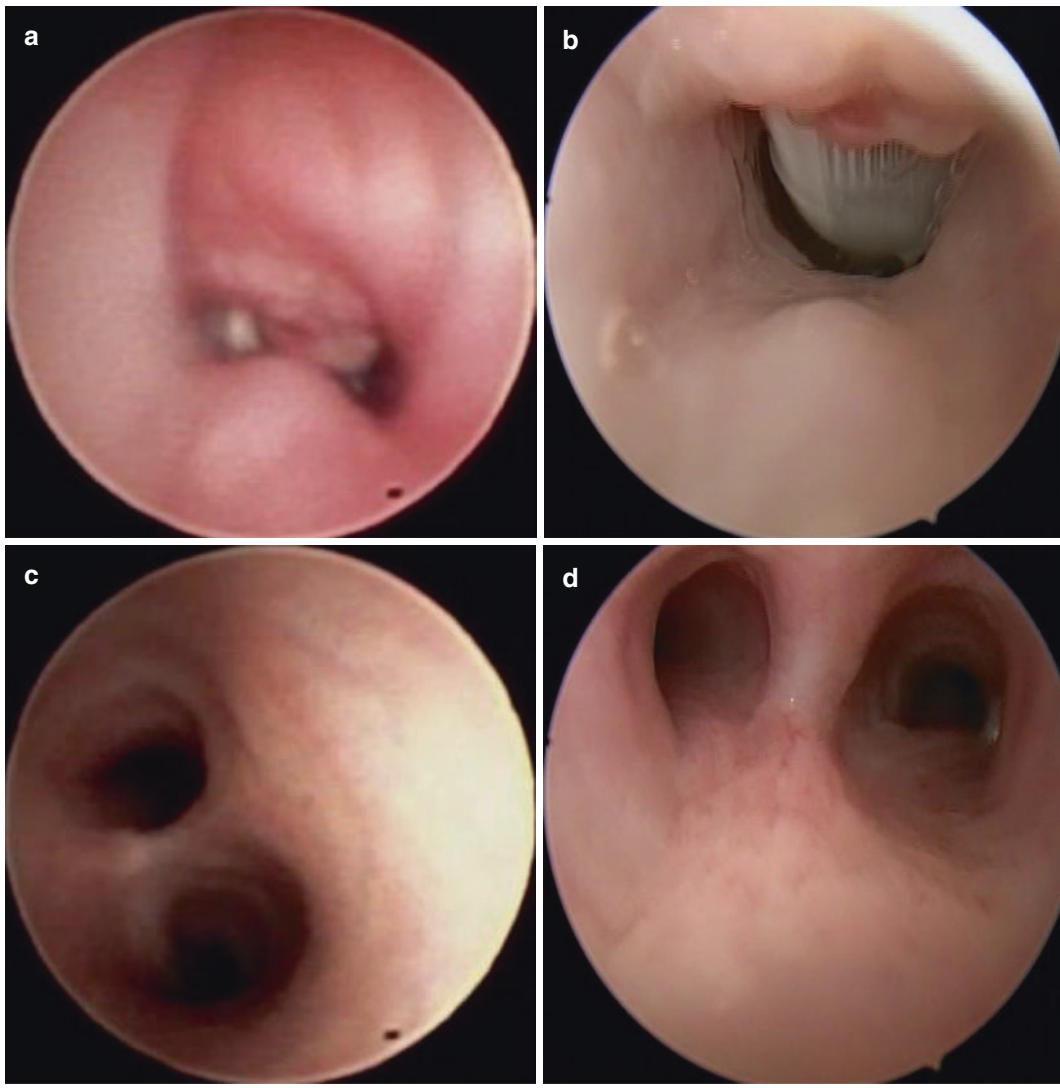

Fig. 17.5 Endoscopic view of the proximal trachea of a patient with a tracheostomy tube from a flexible (**a**) and rigid (**b**) bronchoscopy highlighting suprastomal collapse seen on flexible but not on rigid bronchoscopy. The distal trachea is similar on the flexible (**c**) and rigid (**d**) bronchoscopy

Fluoroscopy

Fluoroscopy is a quick, noninvasive method to assess the lower airway dynamics and is ubiquitously available. Airway fluoroscopy is highly specific but poorly sensitive for evaluating when compared with bronchoscopy [58]. Fluoroscopy is also limited because it may be difficult to distinguish dynamic airway collapse from airway compression and exposes children to radiation.

Multi-detector Computed Tomography

Paired inspiratory and expiratory computed tomography (CT) can be a highly accurate modality to evaluate airway dynamics when compared with bronchoscopy in patients with tracheoesophageal fistulas and esophageal atresia [59]. Young children often require anesthesia and endotracheal intubation to successfully perform inspiratory and expiratory maneuvers, which poses increased risk and can alter airway dynamics. Cine CT permits the evaluation of airway dynamics during spontaneous respiration without sedation, even in young children, and is both sensitive and specific when compared with bronchoscopy [60]. Although cine CT obviates the need for intubation, both paired inspiratory and expiratory CT and cine CT require exposure to ionizing radiation. Recent methods have aimed to limit radiation exposure [61]; nevertheless, ionizing radiation poses increased risk, especially in young children.

Magnetic Resonance Imaging

Cine magnetic resonance imaging (MRI) has shown potential for the evaluation of airway dynamics in small studies of adults and cooperative older children but often requires sedation in younger children to avoid motion artifact [62]. Additionally, the smaller anatomy and higher respiratory rates in young children require higher spatial and temporal resolution than typically achieved by traditional cine MRI. Ultrashort echo-time (UTE) MRI has recently been used to quantitatively assess airway dynamics in neonates and can have good sensitivity and specificity when compared with bronchoscopy [63, 64]. Retrospective respiratory gating permits the ability to discard motion artifact related to bulk motion [65, 66]. As a result, UTE MRI has the potential to assess lower airway dynamics without radiation or sedation, during spontaneous respiration.

Summary

Evaluation of airway dynamics is an important aspect of pediatric flexible bronchoscopy. Findings from bronchoscopy can be used to guide both surgical and medical management of dynamic airway pathology. Consequently, it is critical to reliably obtain an accurate diagnosis. There is currently no universally accepted method for the assessment of airway dynamics in children, and the motion of the airway can change dramatically depending on the conditions of the procedure. Therefore, it will be important to develop a standardized technique that accounts for changes in the airway as well as patient effort.

References

1. Thornton AJ, Morley CJ, Hewson PH, Cole TJ, Fowler MA, Tunnacliffe JM. Symptoms in 298 infants under 6 months old, seen at home. Arch Dis Child. 1990;65:280–5.
2. O'Sullivan BP, Finger L, Zwerdling RG. Use of nasopharyngoscopy in the evaluation of children with noisy breathing. Chest. 2004;125:1265–9.
3. Wright CT, Goudy SL. Congenital laryngomalacia: symptom duration and need for surgical intervention. Ann Otol Rhinol Laryngol. 2012;121:57–60.
4. Roger G, Denoyelle F, Triglia JM, Garabedian EN. Severe laryngomalacia: surgical indications and results in 115 patients. Laryngoscope. 1995;105:1111–7.
5. Schroeck H, Fecho K, Abode K, Bailey A. Vocal cord function and bispectral index in pediatric bronchoscopy patients emerging from propofol anesthesia. Pediatr Pulmonol. 2010;45:494–9.
6. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2012;130:576–84.
7. Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoid-

ectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. Otolaryngol Head Neck Surg. 2009;140:800–8.
8. Ehsan Z, Mahmoud M, Shott SR, Amin RS, Ishman SL. The effects of anesthesia and opioids on the upper airway: a systematic review. Laryngoscope. 2016;126:270–84.
9. Nielson DW, Ku PL, Egger M. Topical lidocaine exaggerates laryngomalacia during flexible bronchoscopy. Am J Respir Crit Care Med. 2000;161:147–51.
10. Antoniades N, Worsnop C. Topical lidocaine through the bronchoscope reduces cough rate during bronchoscopy. Respirology. 2009;14:873–6.
11. Arslan IB, Kose I, Ciger E, Demirhan E, Gumussoy M, Cukurova I. Does topical anesthesia using aerosolized lidocaine inhibit the superior laryngeal nerve reflex? Otolaryngol Head Neck Surg. 2013;149:466–72.
12. Berry RB, Kouchi KG, Bower JL, Light RW. Effect of upper airway anesthesia on obstructive sleep apnea. Am J Respir Crit Care Med. 1995;151:1857–61.
13. Deegan PC, Mulloy E, McNicholas WT. Topical oropharyngeal anesthesia in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 1995;151:1108–12.
14. Evans RG, Crawford MW, Noseworthy MD, Yoo SJ. Effect of increasing depth of propofol anesthesia on upper airway configuration in children. Anesthesiology. 2003;99:596–602.
15. Crawford MW, Rohan D, Macgowan CK, Yoo SJ, Macpherson BA. Effect of propofol anesthesia and continuous positive airway pressure on upper airway size and configuration in infants. Anesthesiology. 2006;105:45–50.
16. Machata AM, Kabon B, Willschke H, Prayer D, Marhofer P. Upper airway size and configuration during propofol-based sedation for magnetic resonance imaging: an analysis of 138 infants and children. Paediatr Anaesth. 2010;20:994–1000.
17. Eastwood PR, Szollosi I, Platt PR, Hillman DR. Collapsibility of the upper airway during anesthesia with isoflurane. Anesthesiology. 2002;97:786–93.
18. Crawford MW, Arrica M, Macgowan CK, Yoo SJ. Extent and localization of changes in upper airway caliber with varying concentrations of sevoflurane in children. Anesthesiology. 2006;105:1147–52; discussion 1145A.
19. Litman RS, Kottra JA, Berkowitz RJ, Ward DS. Upper airway obstruction during midazolam/nitrous oxide sedation in children with enlarged tonsils. Pediatr Dent. 1998;20:318–20.
20. Tagaito Y, Isono S, Nishino T. Upper airway reflexes during a combination of propofol and fentanyl anesthesia. Anesthesiology. 1998;88:1459–66.
21. Mahmoud M, Jung D, Salisbury S, et al. Effect of increasing depth of dexmedetomidine and propofol anesthesia on upper airway morphology in children and adolescents with obstructive sleep apnea. J Clin Anesth. 2013;25:529–41.
22. Mahmoud M, Gunter J, Donnelly LF, Wang Y, Nick TG, Sadhasivam S. A comparison of dexmedetomidine with propofol for magnetic resonance imaging sleep studies in children. Anesth Analg. 2009;109:745–53.
23. Mahmoud M, Radhakrishman R, Gunter J, et al. Effect of increasing depth of dexmedetomidine anesthesia on upper airway morphology in children. Paediatr Anaesth. 2010;20:506–15.
24. Amos JM, Durr ML, Nardone HC, Baldassari CM, Duggins A, Ishman SL. Systematic review of drug-induced sleep endoscopy scoring systems. Otolaryngol Head Neck Surg. 2018;158:240–8.
25. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. Eur Arch Otorhinolaryngol. 2011;268:1233–6.
26. Altintas A, Yegin Y, Celik M, Kaya KH, Koc AK, Kayhan FT. Interobserver consistency of drug-induced sleep endoscopy in diagnosing obstructive sleep apnea using a VOTE classification system. J Craniofac Surg. 2018;29:e140–3.
27. Vroegop AV, Vanderveken OM, Wouters K, et al. Observer variation in drug-induced sleep endoscopy: experienced versus nonexperienced ear, nose, and throat surgeons. Sleep. 2013;36:947–53.
28. Green KK, Kent DT, D'Agostino MA, et al. Drug-induced sleep endoscopy and surgical outcomes: a multicenter cohort study. Laryngoscope. 2019;129:761–70.
29. Yalamanchili R, Mack WJ, Kezirian EJ. Drug-induced sleep endoscopy findings in supine vs nonsupine body positions in positional and nonpositional obstructive sleep apnea. JAMA Otolaryngol Head Neck Surg. 2019;145:159–65.
30. Safiruddin F, Koutsourelakis I, de Vries N. Analysis of the influence of head rotation during drug-induced sleep endoscopy in obstructive sleep apnea. Laryngoscope. 2014;124:2195–9.
31. Gazzaz MJ, Isaac A, Anderson S, Alsufyani N, Alrajhi Y, El-Hakim H. Does drug-induced sleep endoscopy change the surgical decision in surgically naive non-syndromic children with snoring/sleep disordered breathing from the standard adenotonsillectomy? A retrospective cohort study. J Otolaryngol Head Neck Surg. 2017;46:12.
32. Donnelly LF, Casper KA, Chen B, Koch BL. Defining normal upper airway motion in asymptomatic children during sleep by means of cine MR techniques. Radiology. 2002;223:176–80.
33. Isaiah A, Kiss E, Olomu P, Koral K, Mitchell RB. Characterization of upper airway obstruction using cine MRI in children with residual obstructive sleep apnea after adenotonsillectomy. Sleep Med. 2018;50:79–86.
34. Clark C, Ulualp SO. Multimodality assessment of upper airway obstruction in children with persistent obstructive sleep apnea after adenotonsillectomy. Laryngoscope. 2017;127:1224–30.
35. Boogaard R, Huijsmans SH, Pijnenburg MW, Tiddens HA, de Jongste JC, Merkus PJ. Tracheomalacia and bronchomalacia in children: incidence and patient characteristics. Chest. 2005;128:3391–7.

36. Hysinger EFN, Padula M, Shinohara R, Zhang H, Panitch H, Kawut S. Tracheobronchomalacia is associated with increased morbidity in bronchopulmonary dysplasia. Ann Am Thorac Soc. 2017;14:1428–35.
37. Hysinger E, Friedman N, Jensen E, Zhang H, Piccione J. Bronchoscopy in neonates with severe bronchopulmonary dysplasia in the NICU. J Perinatol. 2019;39(2):263–8.
38. Bass R, Santiago M, Smith L, et al. Bethanechol in Tracheomalacia: two case series and a review of the literature. Pediat Allergy Immunol Pulmonol. 2018;31:180–3.
39. Panitch HB, Keklikian EN, Motley RA, Wolfson MR, Schidlow DV. Effect of altering smooth muscle tone on maximal expiratory flows in patients with tracheomalacia. Pediatr Pulmonol. 1990;9:170–6.
40. Montgomery J, Sau C, Clement W, et al. Treatment of tracheomalacia with aortopexy in children in Glasgow. Eur J Pediatr Surg. 2014;24:389–93.
41. Shieh HF, Smithers CJ, Hamilton TE, et al. Descending aortopexy and posterior tracheopexy for severe tracheomalacia and left mainstem bronchomalacia. Semin Thorac Cardiovasc Surg. 2019;31(3):479–85.
42. Vondrys D, Elliott MJ, McLaren CA, Noctor C, Roebuck DJ. First experience with biodegradable airway stents in children. Ann Thorac Surg. 2011;92:1870–4.
43. Croteau JR, Cook CD. Volume-pressure and length-tension measurements in human tracheal and bronchial segments. J Appl Physiol. 1961;16:170–2.
44. Panitch HB, Deoras KS, Wolfson MR, Shaffer TH. Maturational changes in airway smooth muscle structure-function relationships. Pediatr Res. 1992;31:151–6.
45. Deoras KS, Wolfson MR, Searls RL, Hilfer SR, Shaffer TH. Developmental changes in tracheal structure. Pediatr Res. 1991;30:170–5.
46. Trachsel D, Erb TO, Frei FJ, Hammer J, Swiss Paediatric Respiratory Research G. Use of continuous positive airway pressure during flexible bronchoscopy in young children. Eur Respir J. 2005;26:773–7.
47. Hsia D, DiBlasi RM, Richardson P, Crotwell D, Debley J, Carter E. The effects of flexible bronchoscopy on mechanical ventilation in a pediatric lung model. Chest. 2009;135:33–40.
48. Davis S, Jones M, Kisling J, Angelicchio C, Tepper RS. Effect of continuous positive airway pressure on forced expiratory flows in infants with tracheomalacia. Am J Respir Crit Care Med. 1998;158:148–52.
49. Panitch HB, Allen JL, Alpert BE, Schidlow DV. Effects of CPAP on lung mechanics in infants with acquired tracheobronchomalacia. Am J Respir Crit Care Med. 1994;150:1341–6.
50. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography: methods, reproducibility, and normal values. Chest. 2009;135:391–400.
51. Wallis C, Alexopoulou E, Anton-Pacheco JL, et al. ERS statement on tracheomalacia and bronchomalacia in children. Eur Respir J. 2019;54(3):1900382.
52. Masters IB, Zimmerman PV, Pandeya N, Petsky HL, Wilson SB, Chang AB. Quantified tracheobronchomalacia disorders and their clinical profiles in children. Chest. 2008;133:461–7.
53. Masters IB, Eastburn MM, Wootton R, et al. A new method for objective identification and measurement of airway lumen in paediatric flexible videobronchoscopy. Thorax. 2005;60:652–8.
54. Majid A, Gaurav K, Sanchez JM, et al. Evaluation of tracheobronchomalacia by dynamic flexible bronchoscopy. A pilot study. Ann Am Thorac Soc. 2014;11:951–5.
55. Wood RE. Evaluation of the upper airway in children. Curr Opin Pediatr. 2008;20:266–71.
56. Choi J, Dharmarajan H, Yu J, et al. Diagnostic flexible versus rigid bronchoscopy for the assessment of tracheomalacia in children. J Laryngol Otol. 2018;132(12):1–5.
57. Hysinger EB, Hart CK, Burg G, De Alarcon A, Benscoter D. Differences in flexible and rigid bronchoscopy for assessment of tracheomalacia. Laryngoscope. 2020; https://doi.org/10.1002/lary.28656.
58. Sanchez MO, Greer MC, Masters IB, Chang AB. A comparison of fluoroscopic airway screening with flexible bronchoscopy for diagnosing tracheomalacia. Pediatr Pulmonol. 2012;47:63–7.
59. Ngerncham M, Lee EY, Zurakowski D, Tracy DA, Jennings R. Tracheobronchomalacia in pediatric patients with esophageal atresia: comparison of diagnostic laryngoscopy/bronchoscopy and dynamic airway multidetector computed tomography. J Pediatr Surg. 2015;50:402–7.
60. Goo HW. Free-breathing cine CT for the diagnosis of tracheomalacia in young children. Pediatr Radiol. 2013;43:922–8.
61. Lee EY, Strauss KJ, Tracy DA, Bastos M, Zurakowski D, Boiselle PM. Comparison of standard-dose and reduced-dose expiratory MDCT techniques for assessment of tracheomalacia in children. Acad Radiol. 2010;17:504–10.
62. Faust RA, Remley KB, Rimell FL. Real-time, cine magnetic resonance imaging for evaluation of the pediatric airway. Laryngoscope. 2001;111:2187–90.
63. Bates AJ, Higano NS, Hysinger EB, et al. Quantitative assessment of regional dynamic airway collapse in neonates via retrospectively respiratory-gated (1) H Ultrashort Echo Time MRI. J Magn Reson Imaging. 2019;49(3):659–67.
64. Hysinger EB, Bates AJ, Higano NS, et al. Ultrashort echo-time MRI for the assessment of tracheomalacia in neonates. Chest. 2020;157(3):595–602.
65. Higano NS, Hahn AD, Tkach JA, et al. Retrospective respiratory self-gating and removal of bulk motion in pulmonary UTE MRI of neonates and adults. Magn Reson Med. 2017;77:1284–95.
66. Hahn AD, Higano NS, Walkup LL, et al. Pulmonary MRI of neonates in the intensive care unit using 3D ultrashort echo time and a small footprint MRI system. J Magn Reson Imaging. 2017;45:463–71.

18 Extrinsic Compression of Lower Airway

Maki Ishizuka and Ernst Eber

Introduction

Almost any process that causes a space occupying mass within the mediastinum or the enlargement or malposition of a vascular structure can lead to airway compression. Lower airway compression should be suspected when stridor or wheezing persist (expiratory) wheezing is localized and monophonic, presents at an atypical age for asthma, or is refractory to treatment. Other signs, symptoms, and complications of central airway compression include episodic apnea ("dying spells"), brassy or barking cough, dyspnea, feeding difficulties, and recurrent or prolonged respiratory infections due to retention of secretions [1]. Cardiac compression due to a mediastinal mass may also result in extrapulmonary symptoms such as syncope or superior vena cava syndrome.

Vascular Anomalies

Congenital vascular anomalies causing tracheoesophageal compression are estimated to occur in 3% of the population based on autopsy studies. However, the majority of these patients are asymptomatic. Symptomatic patients most commonly present with stridor or wheezing, but may also exhibit episodic apnea, croupy cough, recurrent respiratory infections, and dysphagia [2]. The classically described vascular causes of lower airway compression include double aortic arch, right aortic arch with aberrant left subclavian artery and left-sided ductus arteriosus or ligamentum arteriosum, pulmonary artery sling, and innominate artery compression syndrome.

Complete Vascular Rings

Vascular rings completely encircle the trachea and esophagus and are commonly associated with significant symptoms. The most common cause of a vascular ring is double aortic arch, and the second most common is a right aortic arch with an aberrant left subclavian artery and a left-sided ductus arteriosus or ligamentum arteriosum. However, any configuration with a contralaterally descending aorta or diverticulum or dimple will create a vascular ring. The double aortic arch has persistent right and left aortic arches surrounding the trachea and esophagus, compressing both

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_18

(Fig. 18.1). Thus, feeding may cause "blue spells" or "dying spells" as food in the esophagus may further compress the malacic trachea. The arches rejoin to form a common descending aorta on the left-hand side, resulting in a complete encircling of trachea and esophagus. Double aortic arch is also the most common symptomatic vascular anomaly. In a right aortic arch with an aberrant left subclavian artery and left-sided ductus arteriosus or ligamentum arteriosum, the ductus arteriosus arises posteriorly in the mediastinum at the origin of the aberrant left subclavian artery, then courses anteriorly to the left of the trachea and connects to the pulmonary artery. The trachea and esophagus are completely encircled by the right-sided aortic arch, the base of the left subclavian artery and ductus arteriosus, resulting in a complete vascular ring. However, this ring is frequently loose and thus may be asymptomatic.

Pulmonary Artery Sling

Vascular anomalies that do not completely encircle the trachea and esophagus are often asymptomatic. The most symptomatic of the noncircumferential vascular causes of airway compression is pulmonary artery sling. In a pulmonary artery sling, the left pulmonary artery arises from the right pulmonary artery rather than from the main pulmonary artery and passes between the lower trachea and esophagus as it courses toward the left lung. The resultant sling compresses the distal trachea (Fig. 18.2). Pulmonary artery sling is the only vascular anomaly to course between the trachea and esophagus; therefore, compression will be seen on the posterior tracheal wall. The right mainstem bronchus may also be compressed as the aberrant left pulmonary artery crosses over it. A pulmonary artery sling is frequently associated with tracheal stenosis, typically of a funnel-like shape ("rat-tail" trachea).

Innominate Artery Compression Syndrome

The innominate artery normally crosses from left to right along the anterior trachea from its origin on the aortic arch to right of the midline. Anterior tracheal compression has been reported in 30% of children younger than 2 years of age, most of whom are asymptomatic [3].

Diagnosis, Treatment, and Prognosis

Initial screening with frontal and lateral radiographs may provide important findings such as uni- or bilateral hyperinflation, location of obstruction, or structural abnormalities to suggest extrin-

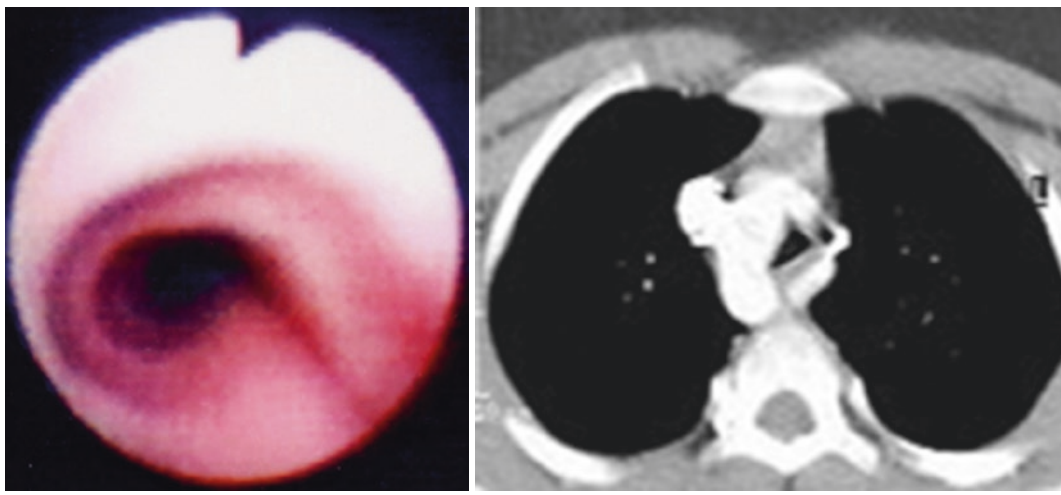

Fig. 18.1 Compression of trachea due to double aortic arch. (*Left*: From von Mutius et al. [13])

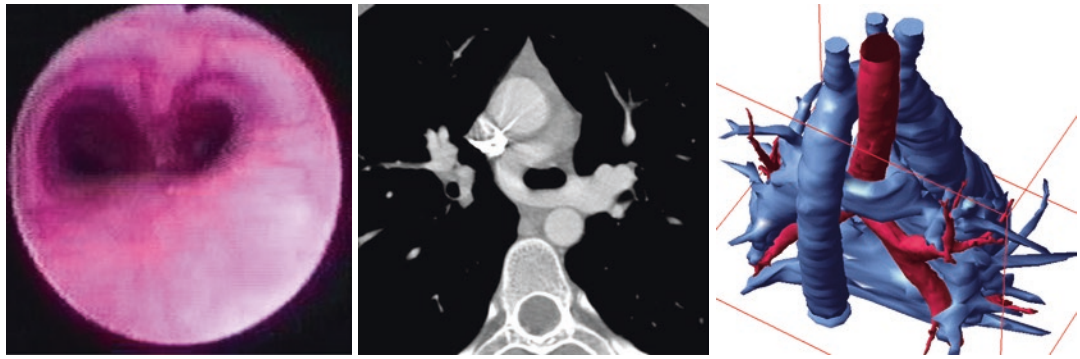

Fig. 18.2 Compression of trachea due to pulmonary artery sling

sic airway compression. The registration of (tidal and) maximal flow-volume curves allows distinction between extra- and intrathoracic airway obstruction and between variable (tracheomalacia) and fixed (tracheal stenosis) obstruction. The diagnosis of vascular anomalies can often be made by a barium swallow, which identifies the esophageal compression(s). Flexible bronchoscopy is preferred over rigid bronchoscopy, as it can be done with only minimal mechanical distortion of the airway anatomy and dynamics; it is mandatory that evaluation of airway dynamics is performed during spontaneous breathing [1]. Bronchoscopy will identify a pulsatile compression of the airway, with more pronounced pulsations when systemic arteries are involved. There are typical findings for various anomalies of the heart and large vessels corresponding to their anatomical relationship with the central airways [4]. It is important to note that any vascular anomaly causing tracheomalacia can be associated with tracheoesophageal fistulas or other forms of tracheal stenosis, such as complete tracheal rings, that should be diagnosed prior to any definitive surgical procedure [5]. Although the endoscopic picture may be strongly suggestive of the cause of airway obstruction, the diagnostic procedures of choice to delineate the anatomy in detail are a computed tomography (CT) angiogram of the chest and great vessels or a magnetic resonance angiogram (MRA). Symptoms of tracheal compression typically improve following surgical repair. However, acquired tracheomalacia and bronchomalacia very often continue to cause symptoms after the extrinsic compression has been removed. Generally, in patients with isolated tracheomalacia or bronchomalacia airway function improves with age, as the airway grows and the airway wall stiffens [1].

Cardiac Disease

Enlargement of cardiac structures can cause airway compression. These include enlargement of the ascending aorta, such as is seen in Marfan syndrome; enlargement of the pulmonary arteries, as in congenital absence of the pulmonary valve; or enlargement of the left atrium.

Cardiac diseases with large left-to-right intracardiac shunts such as ventricular septal defect, or patent ductus arteriosus can result in dilated pulmonary arteries and compression of the tracheobronchial tree. Sites of compression can be seen at the left main bronchus, the left upper lobe bronchus, the junction of the right bronchus intermedius and right middle lobe bronchus, and the left side of the distal trachea [4, 6].

Mediastinal Mass

Mediastinal masses, particularly in the anterior or superior mediastinum can cause compression of the trachea or bronchi, resulting in chronic cough, persistent or progressive wheeze or stridor, or dyspnea. These masses include lymphomas, teratomas, thymomas, lipomas, vascular tumors, and bronchogenic cysts.

Unlike in adults, large masses can cause life-threatening airway compression because of the

combination of the smaller airway size and greater compressibility of the pediatric airway. Although tracheal obstruction may not be apparent on presentation, children who are unable to lie supine because of increased dyspnea are at high risk for complete tracheal obstruction. Children with a mediastinal mass may also present with extrapulmonary symptoms from cardiac compression such as syncope, jugular venous distention, or superior vena cava syndrome; or constitutional symptoms such as fever, night sweats, and weight loss.

Chest radiograph may reveal a mediastinal mass, prominent hilar lymph nodes, posterior tracheal deviation, atelectasis, or pleural effusion. Flexible bronchoscopy demonstrates the site and extent of airway obstruction. Transbronchial needle aspiration with endobronchial ultrasound (EBUS) can be performed at institutions with highly experienced bronchoscopy and anesthesiology teams for mediastinal or hilar lesions to diagnose leukemia, lymphoma, sarcoidosis, and tuberculosis [7].

Lymphoma

The most common mediastinal mass in children are lymphomas, accounting for about 45% of all anterior mediastinal masses. One-third of the lymphomas are Hodgkin lymphomas and two-thirds are non-Hodgkin lymphomas. Non-Hodgkin lymphoma is more likely to occur in younger children, while Hodgkin lymphoma tends to occur in adolescent populations.

Teratoma

The next most common is teratoma, accounting for about 25% of all anterior mediastinal masses. Mediastinal teratomas are often present at birth, and many are now detected prenatally. However, there are multiple reports of large masses discovered only in adulthood. Benign cystic teratomas (mediastinal dermoid cyst) contain such elements of ectodermal tissue as hair, sweat glands, sebaceous cysts, and teeth. These masses cause symptoms because of pressure on, or erosion into, the adjacent respiratory structures. Symptoms usually include vague chest discomfort associated with cough, dyspnea, and pneumonitis. Infection may cause a sudden exacerbation of symptoms, and rupture of the cyst into the lung may occur with expectoration of hair and other materials.

Thymoma

The normal pediatric thymus is absolutely and relatively larger than that in adults. The large thymus in infancy is sometimes mistaken for true pathology. Thymus lesions such as benign thymic tumors (thymoma), malignant thymus tumors, and thymic cysts are rare; however, they can cause compression of the lung or airway. Thymic cysts can be located anywhere between the pyriform sinus and the anterior mediastinum. Thymic hyperplasia is also a rare disorder of unknown etiology; the thymus is markedly enlarged without disruption of the normal architecture. Enlarged thymus rarely can compress vital structures.

Vascular Tumor

Vascular-lymphatic abnormalities of the mediastinum may be classified as cavernous hemangioma, hemangiopericytoma, angiosarcoma, or lymphangioma (cystic hygroma). Vascular tumors isolated to the mediastinum in children are rare, and they may occur at any level in the mediastinum but are more frequent in the upper portion of the thorax and in the anterior mediastinum.

Bronchogenic Cyst

Bronchogenic cysts are foregut-derived cystic malformations of the respiratory tract. These are usually located in the middle mediastinum and asymptomatic. When the bronchogenic cyst is located just below the carina, it may cause severe respiratory distress due to compression of either one or both major bronchi. Bronchogenic cysts may communicate with the tracheobronchial tree and show varying air-fluid levels accompanied by the expectoration of purulent material. Further, a small risk of malignancy has been reported.

Lymphadenopathy/Lymphadenitis

Tuberculosis

Tuberculous mediastinal lymphadenitis is a frequent manifestation of primary pulmonary tuberculosis and is caused by the formation of tuberculous caseating granulomas in lymph nodes. While enlarged nodes occur in 83–96% of pediatric cases, the prevalence of lymphadenopathy decreases with increasing age [8]. Incidence of complicated lymph node disease varies from 8% to 38%; however, the exact incidence of children with airway obstruction caused by primary tuberculosis is unknown [9]. Lymph node involvement is mostly unilateral, with the hilar and paratracheal regions being most commonly involved, followed by the subcarinal nodes. Segmental or lobar atelectasis, pneumonia, hyperinflation, cavities, or mucoid impaction distal to the obstructed bronchus may be seen. Hilar lymphadenopathy can cause compression of the bronchus intermedius and left main bronchus. The commonest site of airway compression is the bronchus intermedius, which is compressed between the right hilar lymphadenopathy and subcarinal lymphadenopathy, resulting in collapse of the right middle and right lower lobes [10, 11].

Histoplasmosis

Enlarged mediastinal lymph nodes commonly accompany pulmonary infiltrates in the course of acute and subacute pulmonary histoplasmosis. The inflamed nodes may compress nearby anatomic structures, characteristically leading to chest pain from mediastinal distention, chronic cough, or atelectasis from bronchial compression, dysphagia from esophageal compression or venous congestion from superior vena cava obstruction. Due to smaller and more pliable airways, children are at higher risk of airway compression. Mediastinal lymphadenitis with histoplasmosis tends to affect younger patient populations. In histoplasmosis, mediastinal granuloma, an amalgamated mass of necrotic mediastinal lymph nodes, often paratracheal or subcarinal in location, can grow up to 10 cm in size to compromise the airway. Mediastinal fibrosis, an abnormal and exuberant fibrotic response to past infection, is a rare complication of histoplasmosis. This leads to encasement of mediastinal structures and impingement of the esophagus, airways, and great vessels, including the pulmonary artery and superior vena cava [12].

References

1. Wallis C, Alexopoulou E, Antón-Pacheco JL, et al. ERS statement on tracheomalacia and bronchomalacia in children. Eur Respir J. 2019;54(3):1900382.
2. Erwin EA, Gerber ME, Cotton RT. Vascular compression of the airway: indications for and results of surgical management. Int J Pediatr Otorhinolaryngol. 1997;40(2–3):155–62.
3. Strife JL, Baumel AS, Dunbar JS. Tracheal compression by the innominate artery in infancy and childhood. Radiology. 1981;139(1):73–5.
4. Holinger LD, Lusk RP, Green CG, editors. Pediatric laryngology and bronchoesophagology. Philadelphia: Lippincott-Raven; 1997.
5. Rimell FL, Stool SE. Diagnosis and management of pediatric tracheal stenosis. Otolaryngol Clin N Am. 1995;28(4):809–27.
6. Berlinger NT, Long C, Foker J, Lucas RV. Tracheobronchial compression in acyanotic congenital heart disease. Ann Otol Rhinol Laryngol. 1983;92(4 Pt 1):387–90.
7. Eber E, Antón-Pacheco JL, de Blic J, et al. ERS statement: interventional bronchoscopy in children. Eur Respir J. 2017;50(6):1700901.
8. Kim HY, Song KS, Goo JM, Lee JS, Lee KS, Lim TH. Thoracic sequelae and complications of tuberculosis. Radiographics. 2001;21(4):839–58; discussion 859–60.
9. Goussard P, Gie R. Airway involvement in pulmonary tuberculosis. Paediatr Respir Rev. 2007;8(2):118–23.
10. Arora A, Bhalla AS, Jana M, Sharma R. Overview of airway involvement in tuberculosis. J Med Imaging Radiat Oncol. 2013;57(5):576–81.
11. Lucas S, Andronikou S, Goussard P, Gie R. CT features of lymphobronchial tuberculosis in children, including complications and associated abnormalities. Pediatr Radiol. 2012;42(8):923–31.
12. Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin N Am. 2016;30(1):207–27.
13. Eber E. Fehlbildungen der Atemwege. In: von Mutius E, Gappa M, Eber E, Frey U, editors. Pädiatrische Pneumologie. 3rd ed. Berlin Heidelberg: Springer; 2014. p. 356–76. (ISBN 978-3-642-34826-6).

Pneumonia: Immunocompetent Children

19

Timothy J. Vece and Erin Nicole Worthington

Introduction

Pneumonia is an infection of the lower airways (alveoli and distal bronchi) and is commonly caused by bacteria or viruses in immunocompetent children, with fungi and mold being less important, but still occasional pathogens. Despite advances in antimicrobial therapy, pneumonia remains one of the leading causes of morbidity and mortality in children, both the United States and worldwide [1, 2]. Pneumonia is usually diagnosed based on age and clinical presentation and treated empirically with either appropriate antimicrobials or supportive care, without need for imaging or advanced diagnostic testing. In cases of severe disease, recurrent or chronic symptoms, or if patients are recalcitrant to standard therapy, radiographic imaging can provide corroboration of clinic symptoms and evaluate for complications. In these situations, identification of the causative pathogen is important to guide medical therapy. It is in these cases that flexible bronchoscopy can be utilized to obtain samples from the lower airway for pathogen identification. This chapter will focus on the causes of pneumonia in immunocompetent children and the role flexible of bronchoscopy in the diagnosis and treatment of pneumonia.

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Community-Associated Pneumonia

Community-acquired pneumonia (CAP) is defined as the acute onset of the signs and symptoms consistent with a lower respiratory tract infection in the outpatient setting. In the United States, there are approximately 1.5 million cases of pediatric CAP diagnosed annually with almost 8% of childhood CAP cases requiring hospital admission [3]. The highest incidence of childhood pneumonia is found in children under 5 years of age [4–9].

Common Community-Associated Pneumonia Pathogens

CAP is a heterogeneous disease caused by both viral and bacterial pathogens (Table 19.1) [10]. CAP was historically considered primarily a bacterial process; however, with the advent of pneumococcal and *Haemophilus influenzae* vaccinations, along with improved detection methods, viral pathogens are now recognized as the primary etiology of CAP, either as a sole pathogen or as a coinfection [9, 11–13]. Studies identifying the microorganisms responsible for childhood CAP found that cases of viral pneu-

S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_19

Table 19.1 Common microorganisms identified in childhood pneumonia

Viruses	Bacteria	Atypical Bacteria
Respiratory syncytial virus	*Streptococcus pneumoniae*	*Mycoplasma pneumoniae*
Rhinovirus	*Staphylococcus aureus*	*Chlamydophila pneumonia*
Bocavirus	Viridans group streptococci	
Parainfluenza virus 1, 2, 3, 4	*Streptococcus pyogenes*	
Human metapneumovirus	*Haemophilus influenzae*	
Adenovirus	*Moraxella catarrhalis*	
Influenza virus		
Coronavirus		

monia ranged from 62% to 87.5%, bacterial pneumonia ranged from 8% to 53%, and bacterial-viral coinfection ranged from 7% to 30% [9, 11–13]. The viruses most commonly identified were respiratory syncytial virus, rhinovirus, bocavirus, parainfluenza viruses, human metapneumovirus, adenovirus, influenza virus, and coronavirus [9, 11–13] (Table 19.1). An increased ability to detect viral pathogens due to increased sensitivity and the use of polymerase chain reaction (PCR)-based respiratory viral pathogen tests is likely the reason for increased identification of viral pathogens are in community-acquired pneumonia [14]. Outside of the newborn period, *Streptococcus pneumoniae* is the most common bacterial pathogen involved in childhood pneumonia with an incidence of 3–4% across all age groups [9, 15, 16]. Another common cause of CAP is *Mycoplasma pneumoniae,* with a peak incidence in school-aged children [17]. *Staphylococcus aureus,* viridans group *streptococci*, and *Streptococcus pyogenes* were the next most frequent cause of bacterial pneumonia [9, 11–13]. Less commonly isolated bacteria are *Chlamydophila pneumoniae*, *Haemophilus influenzae*, and other Gram-negative bacteria [9, 11–13].

Complications of severe pneumonia include parapneumonic effusion, empyema, lung abscess, pneumatocele, and necrotizing pneumonia [18]. Parapneumonic effusions are highly associated with *Streptococcus pneumoniae, Streptococcus pyogenes, or Staphylococcus aureus* infections [19–21]. A rarer complication is necrotizing pneumonia, which is characterized by necrosis of lung tissue and subsequent cavitation, and is associated with both *Staphylococcus aureus* and *Streptococcus pneumoniae* [22–26]. The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing in the community with a corresponding increase in children hospitalized with a MRSA pneumonia [27, 28]. MRSA pneumonia is associated with more severe disease and higher complication rates in children [27, 28].

Host-Defense and Viral-Bacterial Co-Infection

The most recent epidemiology studies highlight how common both viral and bacterial pathogens are identified in pediatric pneumonia [9, 11–13]. What is not clear is that whether these are true coinfections and what role the pathogens play individually or together with the host defense system. The true clinical consequences of these mixed infections in childhood CAP is not fully understood, but coinfections have been shown to cause a more complicated clinical course with worse outcomes in children [29–32]. The pulmonary host defense system has adapted to utilize physical, mechanical, and immune strategies to maintain a healthy environment and a leading hypothesis is that viral infection alters these defense systems predisposing the airway to a bacterial infection. When the airway epithelium becomes disrupted during a viral infection, there is decreased mucociliary clearance from loss of ciliated cells and dysregulated ciliary beat frequency leading to decreased clearance of airway pathogens [33, 34]. The damaged airway epithelium leads to increased receptor availability resulting in enhanced bacterial adherence [33–38]. Additionally, a dysregulation of mucosal and humoral immunity during an infection can lead to an inability to adequately control both viral and bacterial growth [33, 39]. There is also evidence that the virulence of both bacterial and viral pathogens is enhanced during a coinfection [40]. These alterations in innate and

adaptive immunity during a viral-bacterial coinfection allow for an environment that is primed for bacterial growth. The worse clinical outcome in coinfections is likely due to a dysregulation of innate, mucosal and humoral immunity leading to an inability to adequately control both viral and bacterial growth and possible enhanced pathogen virulence [33–40]. Due to increased recognition of viral-bacterial coinfection, it is often necessary to seek additional causes of worsening clinical status of patients with presumed viral pneumonia. In cases of viral pneumonia where patients are not improving as expected, flexible bronchoscopy can be a useful diagnostic tool to help identify bacterial coinfection.

Diagnosis of Community-Associated Pneumonia

The diagnosis of pneumonia can be challenging and it is a combination of clinical signs and symptoms that help determine if a patient has pneumonia [41–44]. The clinical signs and symptoms observed in pneumonia can include fever, cough, auscultatory abnormalities, tachypnea, dyspnea, increased work of breathing, hypoxemia, anorexia, chest pain, and abdominal pain [9, 45–49]. However, a confirmation of pneumonia requires a chest radiograph with a new pulmonary infiltrate [9, 45–50]. The role of the chest radiograph in pneumonia is to evaluate the extent of the disease, detect complications, evaluate for alternative diagnoses, or guide therapy or medical management [51, 52]. The use of chest radiographs in diagnosing CAP may reduce the use of antibiotics [53]. Abnormal chest radiographs in cases of suspected pneumonia are associated with more severe disease and treatment failure [54, 55].

Radiographic testing can be helpful in confirming a diagnosis of pneumonia and determining the extent of the disease, but has limited utility in specifically identifying if the patient has a viral or bacterial pneumonia [56]. Common chest radiographic findings of pneumonia include interstitial infiltrates, alveolar infiltrates, or lobar consolidations. Classic bacterial pneumonia radiographs show alveolar or lobar infiltrates and may or may not have associated pleural effusion (Fig. 19.1). Most children with lobar infiltrates or pleural effusions will have bacterial pneumonia [16, 56, 57]. Viral pneumonia can present with chest radiographs with alveolar infiltrates or interstitial infiltrates [56]. However, interstitial infiltrates on chest X-ray can be seen equally in bacterial or viral pneumonia [57]. When pneumonia is due to atypical bacteria, such as *Mycoplasma pneumoniae,* chest radiographs commonly have bilateral reticular and interstitial infiltrates early in infection, followed by patchy consolidation with associated pleural effusion and hilar adenopathy [58–60]. Thus, chest radiographs can confirm a diagnosis of pneumonia but cannot conclusively determine the causative pathogen.

Complications seen in severe pneumonia include parapneumonic effusions, abscesses, cavitation, necrotizing pneumonia, and pneumatoceles, and are usually seen in severe bacterial pneumonia (Fig. 19.2) [24, 25]. Computed tomography (CT) of the chest is the imaging modality of choice for diagnosing complications of pneumonia in children [61], and is primarily used when complications are suspected, when a child is not responding to therapy, or if there is difficultly in differentiating suspected pneumonia from other pulmonary pathology. CT of the chest has been showing to be sensitive and accurate and can demonstrate pathology before it becomes apparent on chest X-ray [62, 63]. Intravenous contrast can be used to help identify mediastinal structures and enhance lung abscesses, unless contraindicated due to allergy or renal disease.

Generally, children with CAP usually improve with either supportive care or after starting empiric antibiotics depending if the etiology of the pneumonia is viral or bacterial, respectively. Possible causes of failure of standard therapies include antibiotic resistance, a nonbacterial etiology (viral or fungal), or the presence of complications such as an empyema or pulmonary abscess. Other considerations to take into account would be the possibility of a bronchial obstruction (mucus plug, foreign body, and external bronchial compression), aspiration pneumonia, or other predisposing immune or pulmonary diseases. In cases of severe disease,

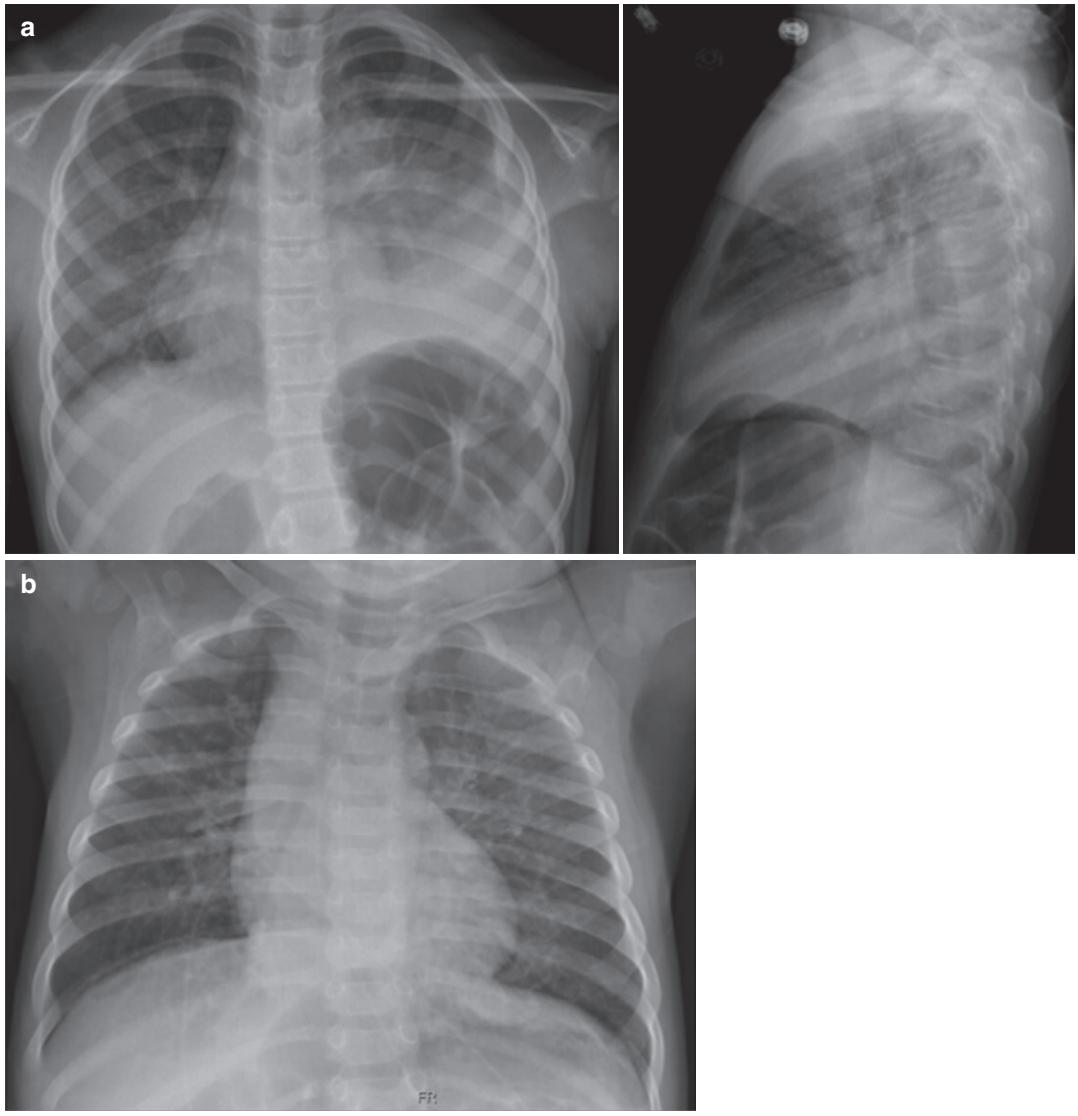

Fig. 19.1 (**a**), Anteroposterior and lateral chest radiograph showing dense consolidation of the left lower lobe. (**b**), Chest radiograph of viral pneumonia showing bilateral interstitial infiltrates

recurrent or chronic symptoms, or nonresponse to antimicrobial therapies, obtaining a specimen from the lower airways for gram stain, culture, and nonculture-based diagnostic testing can aid in diagnosis. The easiest way this is done is by obtaining an expectorated sputum sample. It is not always possible in pediatric patients, however, to obtain an adequate sample, as most children are not able to properly expectorate sputum. A more common method of obtaining a specimen from the lower airways is to use flexible bronchoscopy to obtain bronchoalveolar lavage fluid (BALF).

Flexible Bronchoscopy in Community-Associated Pneumonia

Flexible bronchoscopy is considered a safe and well-tolerated procedure in children [64] and is indicated in cases of persistent or recurrent pneumonia that do not respond to antimicrobial therapy,

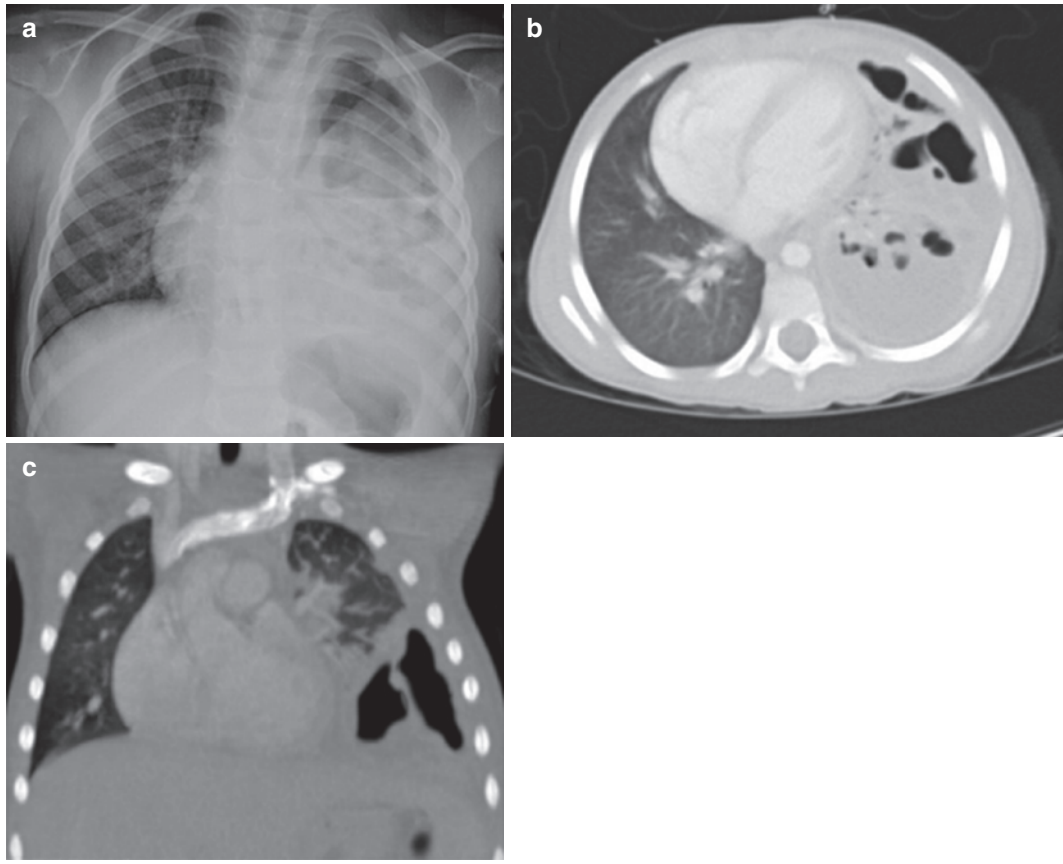

Fig. 19.2 Radiographic imaging of necrotizing pneumonia. (**a**) Chest radiograph showing consolidation of the left lower lobe and lingula with central lucencies. (**b, c**) CT showing consolidation of left lower lobe with multiple areas of cavitation, consistent with necrotizing pneumonia

or in severe disease. Persistent pneumonia is defined as the presence of symptoms of a lower respiratory tract infection and radiological abnormalities in a pediatric patient for longer than a month despite adequate antibiotic therapy [65–67]. Whereas, recurrent pneumonia is defined as having two occurrences of pneumonia over the course of a year or three occurrences of pneumonia over any defined period of time with radiologic clearing in between episodes. Recurrent or persistent pneumonia may be the result of resistant bacteria, unusual or atypical bacterial organisms, a foreign body, aspiration, or an anatomic anomaly. In these cases, flexible bronchoscopy can allow for physical inspection of the airways as well as for the acquisition of BALF for culture and diagnostic testing to identify a causative pathogen.

The visual evaluation of the airways can provide evidence of disease severity. Another purpose of visual examination of the airways is to assess for an anatomical or physical condition predisposing the patient to pneumonia such as mucus plugging, foreign body, or an anatomical airway anomaly such as a tracheal bronchus. The airways in patients with pneumonia can have mucosal edema, erythema, and increased mucus (Fig. 19.3). A chest radiograph or chest CT can help identify the most affected lobe or segment of the lung to direct the best location to perform a bronchoalveolar lavage. If radiographic imaging is not available then the bronchoscopist can identify an optimal area for sample collection by visual inspection for the presence of mucus, erythema, or airway friability which is commonly

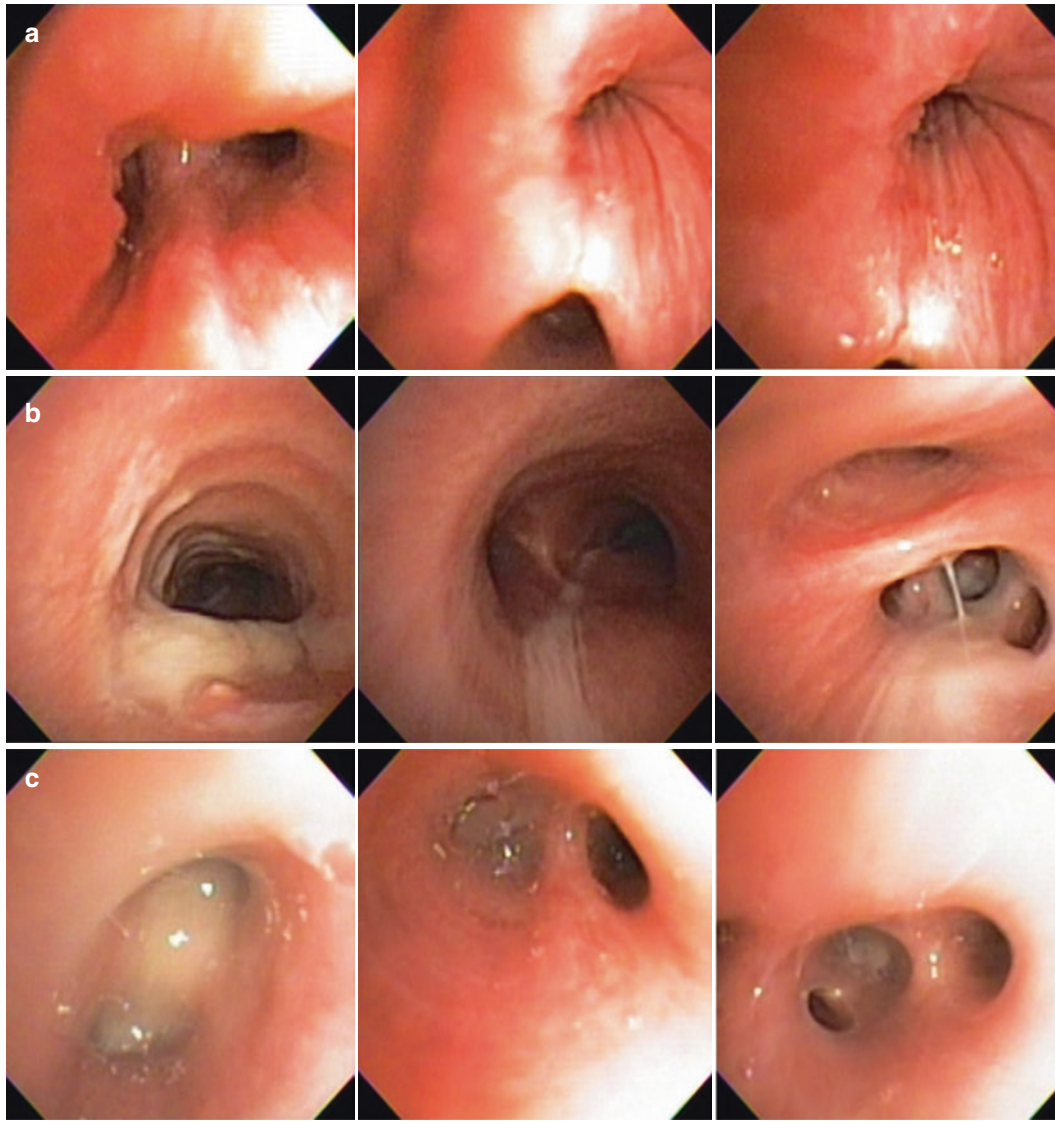

Fig. 19.3 Selected bronchoscopic images. (**a**) Erythema and edema of airway mucosa are common in pneumonia. (**b**) Thick purulent mucus seen streaming up the trachea from the RLL. (**c**) Mucus plugging of various segmental airways

seen in pneumonia (Fig. 19.3). However, the absence of these observations does not exclude a diagnosis of pneumonia.

Diagnostic Testing of Bronchoscopy Specimens

The BALF samples can be obtained in one or more lung segments and either be sent separately or combined before being sent to the laboratory for analysis. BALF can be analyzed for cell count, bacterial culture, fungal culture, acid-fast bacillus (AFB) culture, respiratory viral PCR panel, and cytology depending on the clinical situation. The types and relative percentages of immune cells present in BALF is important information obtained during bronchoscopy in pneumonia. Early viral pneumonia is more likely to have a higher percentage of lymphocytes, while bacterial pneumonia and late viral pneumonia often have a higher percentage of neutrophils in BALF. A high

percentage of eosinophils can be seen in certain fungal and parasitic infections. Quantitative BALF bacterial culture is the definitive diagnostic method for identification of bacterial pathogens. The diagnostic yield of BALF culture for bacterial pneumonia is 30–72% [68–71]. Identification of a pathogen allows for more specific tailoring of antimicrobial therapy, however, BALF cultures can be falsely negative if the pathogen is susceptible to the current antibiotic therapy. Thus, a negative culture result for a patient on empiric antibiotics suggests that the current antibiotic therapy is appropriate. If there is a suspicion for chronic aspiration pneumonia, then the cytology sample can be stained to look for lipid-laden macrophages. *M. pneumoniae* PCR-based testing can be done using BALF, but usually a sample from the upper respiratory tract is used to test for this organism [72]. Testing for *C. pneumoniae* is not recommended, as it is not reliable or readily available. Bronchoscopy is not typically used for diagnosis of viral pneumonia, as samples from the upper respiratory tract are sufficient for testing. However, in the case of a seriously ill patient who is undergoing bronchoscopy, PCR-based viral detection can be performed on BALF.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia is the second most common pediatric nosocomial infection in both the pediatric intensive care unit (PICU) and the neonatal intensive care unit (NICU) [70, 73–76]. Ventilator-associated pneumonia is defined as pneumonia in a mechanically ventilated patient ≥48 hours after being placed on mechanical ventilation. It occurs in 3–10% of PICU patients and up to 6.8–32.3% of NICU patients [75–80]. Ventilator-associated pneumonia is associated with increased morbidity and duration of mechanical ventilation [75–79, 81]. The most common organisms found in children with ventilator-associated pneumonia are *Staphylococcus aureus, Pseudomonas aeruginosa,* and other Gram-negative bacilli [82]. The diagnosis of Ventilator-associated pneumonia by BALF culture has a sensitivity of 50–100% and specificity of 71–100% [70, 71, 83]. Obtaining BALF via flexible bronchoscopy is safe in this patient population and culture data has been shown to change in antibiotic therapy in 36–65% of cases [84]. A diagnostic bronchoscopy is indicated in mechanically ventilated patients with pneumonia if there is no improvement, or slower than expected improvement, on empiric antibiotic therapy.

Unusual Pathogens

There are multiple less common or rare microorganisms that can cause pediatric pneumonia. These organisms include unusual bacterium, fungi, mold, and mycobacterium and are described in detail in a variety of reviews [10, 19]. Many rare pulmonary pathogens typically affect patients that have risk factors, such as under or nonimmunized, immunocompromised patients, aspiration, recent travel, contact with at-risk groups, exposure to animals or geographic endemic areas, or young age. These organisms may include *Legionella pneumophila*, *Mycobacterium tuberculosis*, *Aspergillus fumigatus*, *Pseudomonas Aaeruginosa*, *Burkhoderia cepacia*, *Pneumocystis jiroveci*, and *Cryptococcus neoformans*. If a patient has risk factors and presents with pneumonia, these pathogens should be considered. Certain fungal infections such as histoplasmosis, blastomycosis, and coccidiomycosis, can be seen in immunocompetent children, and in such cases, flexible bronchoscopy can aid in diagnosis.

Fungal Pneumonia

Fungal pathogens account for a small percentage of causes of pediatric pneumonia. Fungal pulmonary infections found in immunocompetent hosts are usually caused by *Histoplasma*, Blastomyces, and Coccidioides which are endemic dimorphic fungi that have a geographic preference. Histoplasmosis is caused by *Histoplasma casulatum* which is endemic in the Ohio and Mississippi river valleys [85, 86]. Coccidioidomycosis is caused by *Coccidioides immitis* and *Coccidioides*

posadasii which are endemic to the central valleys of California, Arizona, New Mexico, Nevada, Northern Mexico, and Central and South America [87, 88]. Blastomycosis is caused by *Blastomyces dermatidis* and *Blastomyces gilchristii*, which are endemic to the Ohio and Mississippi river valleys and the borders of the Great Lakes and the St. Lawrence River [89, 90]. The mechanisms behind pulmonary mycosis include inhalation of fungal spores that are found in the soil and the surrounding natural environment, reactivation of a latent infection, and hematogenous spread. Person to person transmission is not thought to occur in these infections. Fungal pulmonary infections in immunocompetent hosts can have varying presentations that range from asymptomatic nodules to severe multilobar disease and can range in severity from subclinical pneumonia to acute respiratory distress syndrome [87, 91–98].

Fungal pulmonary infections have varied appearances on chest radiographs. Histoplasmosis chest radiographs during an acute infection may be normal, have focal pneumonitis with mediastinal adenopathy, or have extensive interstitial or reticular nodular infiltrates [99]. Chest CT can sometimes show bronchial or vascular compression from lymphadenopathy or granulomas, and in chronic cases, cavitation may be seen [100, 101]. At sites of prior infection, calcified nodules or coin lesions can be seen [100, 101]. In coccidioidomycosis, chest radiographs during an acute infection can range from lobar, nodular, or patchy pulmonary infiltrates and may also have hilar lymphadenopathy [102]. Chest CT imaging can show hilar lymphadenopathy and a tree-in-bud pattern [102]. At sites of prior coccidioidomycosis infection, there may be pulmonary nodules but they do not calcify over time, in contrast to the nodules seen in histoplasmosis [103]. Cavitary lesions can also been seen as a late feature of coccidioidomycosis. Pleural effusions complicate 5–15% of primary pulmonary coccidioidomycosis [96, 104]. Blastomycosis chest radiographic findings include interstitial infiltrates, nodular lesions, lobar consolidation with or without cavitation, and pleural effusion [91, 93, 105]. Hilar and mediastinal lymphadenopathy is uncommon in pulmonary blastomycosis, but lytic bone lesions are also sometimes seen on chest radiographs.

A fungal pulmonary infection often requires a combination of testing modalities for diagnosis. Commonly used tests include fungal culture from the sputum, BALF or tissue; specific fungal antigen detection from blood or urine; antibody titers; and histopathological examination of biopsied pulmonary lesions. The decision of which combination of testing modalities to use for diagnosis varies based on the severity of disease, site of infection, and duration of illness [97, 101, 106, 107]. Bronchoscopy can be used to directly visualize the airways and obtain BALF from the distal airways for direct fungal visualization, culture, and diagnostic testing. Direct examination of the airways in a pulmonary fungal infection can show a variety of airway lesions. In histoplasmosis, there can be airway compression or stenosis from enlarged or calcified lymph nodes, mucosal edema or hyperemia, endobronchial lesions or nodules, broncholiths, or ulcerative lesions (Fig. 19.4) [108]. In coccidioidomycosis, there can be mucosal irregularities, endobronchial nodules or lesions, and extrinsic compression from mediastinal or hilar lymphadenopathy [108]. In blastomycosis mucosal irregularities, edema, increased mucus, and endobronchial lesions have been reported [109, 110]. Histopathological examination of BALF will show histoplasma as a narrow-based budding yeast [101, 106], coccidioides as spherules [107, 111], and blastomyces as thick-walled, broad-based budding yeast [97]. Fungal organisms are often fastidious and can take several weeks to grow in culture media [97, 101, 106, 107, 111]; therefore, antigen testing on BALF, serum, and urine should also be sent while awaiting culture results. It is possible to obtain specific antibody testing in fungal infections; however, positive results often lag behind symptoms in acute infections. Therefore, they are not a practical test for rapid diagnosis. When present, endobronchial lesions can be biopsied using a flexible or rigid bronchoscope and can aid in diagnosis. If biopsied, endobronchial lesion tissue should be sent for histopathology and culture.

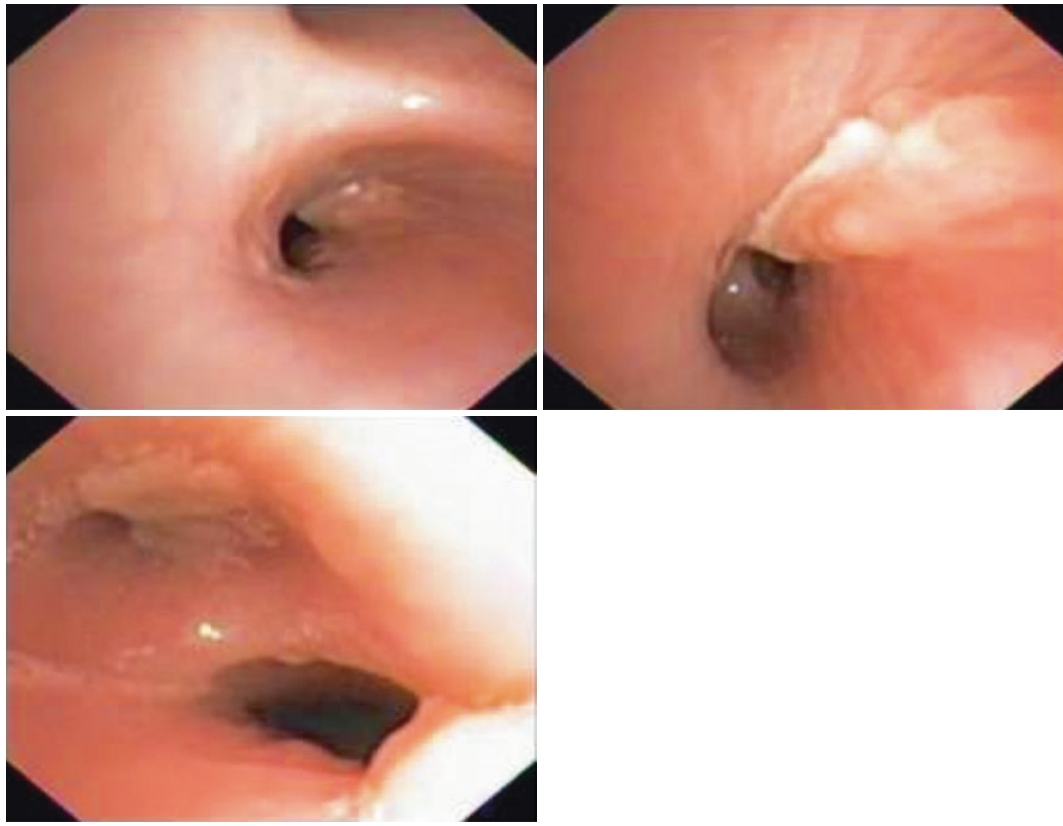

Fig. 19.4 Histoplasma endobronchial lesions seen as granulation tissue narrowing the bronchus intermedius and almost complete obstruction of the right middle lobe

Conclusions

Flexible bronchoscopy is not usually indicated for mild-to-moderate CAP, but it does have an important role in pathogen identification in cases of persistent or recurrent pneumonia in pediatric patients. It is a safe procedure in children which can yield important diagnostic information, often resulting in important changes in medical management [64, 112, 113].

References

1. World Health Organization and Maternal and Child Epidemiology Estimation Group (MCEE). Child causes of death, by Country and by Region. 2000–2017., [cited 2018]. Available from: https://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html.
2. American Lung Association. Trends in pneumonia and influenza: morbidity and mortality. Epidemiology and statistics unit: research and health education division. 2015, [cited 2018]. Available from: https://www.lung.org/assets/documents/research/pi-trend-report.pdf.
3. Kronman MP, et al. Ambulatory visit rates and antibiotic prescribing for children with pneumonia, 1994–2007. Pediatrics. 2011;127:411–8. https://doi.org/10.1542/peds.2010-2008.
4. Madhi SA, et al. The burden of childhood pneumonia in the developed world: a review of the literature. Pediatr Infect Dis J. 2013;32:e119–27. https://doi.org/10.1097/INF.0b013e3182784b26.
5. Dubin PJ, et al. Interleukin-23-mediated inflammation in Pseudomonas aeruginosa pulmonary infection. Infect Immun. 2012;80:398–409. https://doi.org/10.1128/IAI.05821-11.
6. Murphy TF, Henderson FW, Clyde WA Jr, Collier AM, Denny FW. Pneumonia: an eleven-year study in a pediatric practice. Am J Epidemiol. 1981;113:12–21.
7. British Thoracic Society Standards of Care, C. British Thoracic Society Guidelines for the

management of community acquired pneumonia in childhood. Thorax. 2002;57(Suppl 1):i1–24.
8. Jokinen C, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. Am J Epidemiol. 1993;137:977–88.
9. Jain S, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372:835–45. https://doi.org/10.1056/NEJMoa1405870.
10. Katz SE, Williams DJ. Pediatric community-acquired pneumonia in the United States: changing epidemiology, diagnostic and therapeutic challenges, and areas for future research. Infect Dis Clin N Am. 2018;32:47–63. https://doi.org/10.1016/j.idc.2017.11.002.
11. Nascimento-Carvalho AC, et al. Respiratory viruses among children with non-severe community-acquired pneumonia: a prospective cohort study. J Clin Virol. 2018;105:77–83. https://doi.org/10.1016/j.jcv.2018.06.003.
12. Juven T, et al. Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatr Infect Dis J. 2000;19:293–8.
13. Wang M, et al. Incidence of viral infection detected by PCR and real-time PCR in childhood community-acquired pneumonia: a meta-analysis. Respirology. 2015;20:405–12. https://doi.org/10.1111/resp.12472.
14. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet. 2011;377:1264–75. https://doi.org/10.1016/S0140-6736(10)61459-6.
15. McIntosh K. Community-acquired pneumonia in children. N Engl J Med. 2002;346:429–37. https://doi.org/10.1056/NEJMra011994.
16. Michelow IC, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics. 2004;113:701–7.
17. Meyer Sauteur PM, et al. Infection with and carriage of mycoplasma pneumoniae in children. Front Microbiol. 2016;7:329. https://doi.org/10.3389/fmicb.2016.00329.
18. Sawicki GS, Lu FL, Valim C, Cleveland RH, Colin AA. Necrotising pneumonia is an increasingly detected complication of pneumonia in children. Eur Respir J. 2008;31:1285–91. https://doi.org/10.1183/09031936.00099807.
19. Williams DJ, Shah SS. Community-acquired pneumonia in the conjugate vaccine era. J Pediatr Infect Dis Soc. 2012;1:314–28. https://doi.org/10.1093/jpids/pis101.
20. Grijalva CG, Nuorti JP, Zhu Y, Griffin MR. Increasing incidence of empyema complicating childhood community-acquired pneumonia in the United States. Clin Infect Dis. 2010;50:805–13. https://doi.org/10.1086/650573.
21. Grijalva CG, Zhu Y, Nuorti JP, Griffin MR. Emergence of parapneumonic empyema in the USA. Thorax. 2011;66:663–8. https://doi.org/10.1136/thx.2010.156406.
22. Lemaitre C, et al. Necrotizing pneumonia in children: report of 41 cases between 2006 and 2011 in a French tertiary care center. Pediatr Infect Dis J. 2013;32:1146–9. https://doi.org/10.1097/INF.0b013e31829be1bb.
23. Taffarel P, et al. Severe Staphylococcus aureus infection in three pediatric intensive care units: analysis of cases of necrotizing pneumonia. Arch Argent Pediatr. 2014;112:163–8. https://doi.org/10.1590/S0325-00752014000200010.5546/aap.2014.163.
24. Masters IB, Isles AF, Grimwood K. Necrotizing pneumonia: an emerging problem in children? Pneumonia (Nathan). 2017;9:11. https://doi.org/10.1186/s41479-017-0035-0.
25. Erlichman I, et al. Complicated community acquired pneumonia in childhood: different types, clinical course, and outcome. Pediatr Pulmonol. 2017;52:247–54. https://doi.org/10.1002/ppul.23523.
26. Ramphul N, et al. Cavitatory lung disease complicating empyema in children. Pediatr Pulmonol. 2006;41:750–3. https://doi.org/10.1002/ppul.20434.
27. Gerber JS, Coffin SE, Smathers SA, Zaoutis TE. Trends in the incidence of methicillin-resistant Staphylococcus aureus infection in children's hospitals in the United States. Clin Infect Dis. 2009;49:65–71. https://doi.org/10.1086/599348.
28. Carrillo-Marquez MA, et al. Staphylococcus aureus pneumonia in children in the era of community-acquired methicillin-resistance at Texas Children's Hospital. Pediatr Infect Dis J. 2011;30:545–50. https://doi.org/10.1097/INF.0b013e31821618be.
29. Reed C, et al. Infection with community-onset Staphylococcus aureus and influenza virus in hospitalized children. Pediatr Infect Dis J. 2009;28:572–6. https://doi.org/10.1097/INF.0b013e31819d8b71.
30. Finelli L, et al. Influenza-associated pediatric mortality in the United States: increase of Staphylococcus aureus coinfection. Pediatrics. 2008;122:805–11. https://doi.org/10.1542/peds.2008-1336.
31. Thomas P, Riffelmann M, Schweiger B, Dominik S, von Konig CH. Fatal influenza A virus infection in a child vaccinated against influenza. Pediatr Infect Dis J. 2003;22:201–2.
32. Connor E, Powell K. Fulminant pneumonia caused by concomitant infection with influenza B virus and Staphylococcus aureus. J Pediatr. 1985;106:447–50.
33. Bakaletz LO. Viral-bacterial co-infections in the respiratory tract. Curr Opin Microbiol. 2017;35:30–5. https://doi.org/10.1016/j.mib.2016.11.003.
34. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol. 2014;12:252–62. https://doi.org/10.1038/nrmicro3231.
35. Bellinghausen C, Rohde GGU, Savelkoul PHM, Wouters EFM, Stassen FRM. Viral-bacterial interactions in the respiratory tract. J Gen Virol. 2016;97:3089–102. https://doi.org/10.1099/jgv.0.000627.
36. Ballinger MN, Standiford TJ. Postinfluenza bacterial pneumonia: host defenses gone awry. J Interf Cytokine Res. 2010;30:643–52. https://doi.org/10.1089/jir.2010.0049.

37. Li N, et al. Influenza viral neuraminidase primes bacterial coinfection through TGF-beta-mediated expression of host cell receptors. Proc Natl Acad Sci U S A. 2015;112:238–43. https://doi.org/10.1073/pnas.1414422112.
38. Avadhanula V, et al. Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. J Virol. 2006;80:1629–36. https://doi.org/10.1128/JVI.80.4.1629-1636.2006.
39. Braciale TJ, Sun J, Kim TS. Regulating the adaptive immune response to respiratory virus infection. Nat Rev Immunol. 2012;12:295–305. https://doi.org/10.1038/nri3166.
40. McCullers JA. Do specific virus-bacteria pairings drive clinical outcomes of pneumonia? Clin Microbiol Infect. 2013;19:113–8. https://doi.org/10.1111/1469-0691.12093.
41. Margolis P, Gadomski A. The rational clinical examination. Does this infant have pneumonia? JAMA. 1998;279:308–13.
42. Lynch T, et al. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. PLoS One. 2010;5:e11989. https://doi.org/10.1371/journal.pone.0011989.
43. Korppi M. Mixed microbial aetiology of community-acquired pneumonia in children. APMIS. 2002;110:515–22.
44. Korppi M, Don M, Valent F, Canciani M. The value of clinical features in differentiating between viral, pneumococcal and atypical bacterial pneumonia in children. Acta Paediatr. 2008;97:943–7. https://doi.org/10.1111/j.1651-2227.2008.00789.x.
45. Lynch T, Platt R, Gouin S, Larson C, Patenaude Y. Can we predict which children with clinically suspected pneumonia will have the presence of focal infiltrates on chest radiographs? Pediatrics. 2004;113:e186–9.
46. Mathews B, et al. Clinical predictors of pneumonia among children with wheezing. Pediatrics. 2009;124:e29–36. https://doi.org/10.1542/peds.2008-2062.
47. Neuman MI, Monuteaux MC, Scully KJ, Bachur RG. Prediction of pneumonia in a pediatric emergency department. Pediatrics. 2011;128:246–53. https://doi.org/10.1542/peds.2010-3367.
48. Mahabee-Gittens EM, et al. Identifying children with pneumonia in the emergency department. Clin Pediatr (Phila). 2005;44:427–35. https://doi.org/10.1177/000992280504400508.
49. Murphy CG, van de Pol AC, Harper MB, Bachur RG. Clinical predictors of occult pneumonia in the febrile child. Acad Emerg Med. 2007;14:243–9. https://doi.org/10.1197/j.aem.2006.08.022.
50. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36:309–32. https://doi.org/10.1016/j.ajic.2008.03.002.
51. Alario AJ, et al. Usefulness of chest radiographs in children with acute lower respiratory tract disease. J Pediatr. 1987;111:187–93.
52. Grossman LK, Caplan SE. Clinical, laboratory, and radiological information in the diagnosis of pneumonia in children. Ann Emerg Med. 1988;17:43–6.
53. Nelson KA, Morrow C, Wingerter SL, Bachur RG, Neuman MI. Impact of chest radiography on antibiotic treatment for children with suspected pneumonia. Pediatr Emerg Care. 2016;32:514–9. https://doi.org/10.1097/PEC.0000000000000868.
54. Kelly MS, et al. Chest radiographic findings and outcomes of pneumonia among children in Botswana. Pediatr Infect Dis J. 2016;35:257–62. https://doi.org/10.1097/INF.0000000000000990.
55. Simbalista R, Andrade DC, Borges IC, Araujo M, Nascimento-Carvalho CM. Differences upon admission and in hospital course of children hospitalized with community-acquired pneumonia with or without radiologically-confirmed pneumonia: a retrospective cohort study. BMC Pediatr. 2015;15:166. https://doi.org/10.1186/s12887-015-0485-6.
56. Virkki R, et al. Differentiation of bacterial and viral pneumonia in children. Thorax. 2002;57:438–41.
57. Korppi M, Kiekara O, Heiskanen-Kosma T, Soimakallio S. Comparison of radiological findings and microbial aetiology of childhood pneumonia. Acta Paediatr. 1993;82:360–3.
58. Kishaba T. Community-acquired pneumonia caused by mycoplasma pneumoniae: how physical and radiological examination contribute to successful diagnosis. Front Med (Lausanne). 2016;3:28. https://doi.org/10.3389/fmed.2016.00028.
59. Guckel C, Benz-Bohm G, Widemann B. Mycoplasmal pneumonias in childhood. Roentgen features, differential diagnosis and review of literature. Pediatr Radiol. 1989;19:499–503.
60. Nambu A, et al. Chlamydia pneumoniae: comparison with findings of Mycoplasma pneumoniae and Streptococcus pneumoniae at thin-section CT. Radiology. 2006;238:330–8. https://doi.org/10.1148/radiol.2381040088.
61. Andronikou S, Goussard P, Sorantin E. Computed tomography in children with community-acquired pneumonia. Pediatr Radiol. 2017;47:1431–40. https://doi.org/10.1007/s00247-017-3891-0.
62. Hodina M, Hanquinet S, Cotting J, Schnyder P, Gudinchet F. Imaging of cavitary necrosis in complicated childhood pneumonia. Eur Radiol. 2002;12:391–6. https://doi.org/10.1007/s003300101008.
63. Donnelly LF, Klosterman LA. The yield of CT of children who have complicated pneumonia and noncontributory chest radiography. AJR Am J Roentgenol. 1998;170:1627–31. https://doi.org/10.2214/ajr.170.6.9609186.
64. de Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. Eur Respir J. 2002;20:1271–6.

65. Wald ER. Recurrent and nonresolving pneumonia in children. Semin Respir Infect. 1993;8:46–58.
66. Lodha R, Puranik M, Chandra U, Natchu M, Kabra SK. Persistent pneumonia in children. Indian Pediatr. 2003;40:967–70.
67. Lodha R, Puranik M, Natchu UC, Kabra SK. Recurrent pneumonia in children: clinical profile and underlying causes. Acta Paediatr. 2002;91:1170–3.
68. Sanchez Nieto JM, Carillo Alcaraz A. The role of bronchoalveolar lavage in the diagnosis of bacterial pneumonia. Eur J Clin Microbiol Infect Dis. 1995;14:839–50.
69. Gokdemir Y, et al. Bronchoscopic evaluation of unexplained recurrent and persistent pneumonia in children. J Paediatr Child Health. 2013;49:E204–7. https://doi.org/10.1111/jpc.12124.
70. Gauvin F, et al. Ventilator-associated pneumonia in intubated children: comparison of different diagnostic methods. Pediatr Crit Care Med. 2003;4:437–43. https://doi.org/10.1097/01.PCC.0000090290.53959.F4.
71. Labenne M, et al. Blind protected specimen brush and bronchoalveolar lavage in ventilated children. Crit Care Med. 1999;27:2537–43.
72. Waris ME, et al. Diagnosis of Mycoplasma pneumoniae pneumonia in children. J Clin Microbiol. 1998;36:3155–9.
73. CDC definitions for nosocomial infections, 1988. Am Rev Respir Dis. 1989;139:1058–9. https://doi.org/10.1164/ajrccm/139.4.1058.
74. Patra PK, Jayashree M, Singhi S, Ray P, Saxena AK. Nosocomial pneumonia in a pediatric intensive care unit. Indian Pediatr. 2007;44:511–8.
75. Gaynes RP, et al. Nosocomial infections among neonates in high-risk nurseries in the United States. National Nosocomial Infections Surveillance System. Pediatrics. 1996;98:357–61.
76. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in pediatric intensive care units in the United States. National Nosocomial Infections Surveillance System. Pediatrics. 1999;103:e39.
77. Foglia E, Meier MD, Elward A. Ventilator-associated pneumonia in neonatal and pediatric intensive care unit patients. Clin Microbiol Rev. 2007;20:409–25., table of contents. https://doi.org/10.1128/CMR.00041-06.
78. Elward AM, Warren DK, Fraser VJ. Ventilator-associated pneumonia in pediatric intensive care unit patients: risk factors and outcomes. Pediatrics. 2002;109:758–64.
79. Almuneef M, Memish ZA, Balkhy HH, Alalem H, Abutaleb A. Ventilator-associated pneumonia in a pediatric intensive care unit in Saudi Arabia: a 30-month prospective surveillance. Infect Control Hosp Epidemiol. 2004;25:753–8. https://doi.org/10.1086/502472.
80. Fischer JE, Ramser M, Fanconi S. Use of antibiotics in pediatric intensive care and potential savings. Intensive Care Med. 2000;26:959–66.
81. Fischer JE, Allen P, Fanconi S. Delay of extubation in neonates and children after cardiac surgery: impact of ventilator-associated pneumonia. Intensive Care Med. 2000;26:942–9.
82. Babcock HM, et al. Ventilator-associated pneumonia in a multi-hospital system: differences in microbiology by location. Infect Control Hosp Epidemiol. 2003;24:853–8. https://doi.org/10.1086/502149.
83. Cook DJ, Fitzgerald JM, Guyatt GH, Walter S. Evaluation of the protected brush catheter and bronchoalveolar lavage in the diagnosis of nosocomial pneumonia. J Intensive Care Med. 1991;6:196–205. https://doi.org/10.1177/088506669100600405.
84. Shorr AF, Sherner JH, Jackson WL, Kollef MH. Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. Crit Care Med. 2005;33:46–53.
85. Kauffman CA. Histoplasmosis. Clin Chest Med. 2009;30:217–25., v. https://doi.org/10.1016/j.ccm.2009.02.002.
86. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev. 2007;20:115–32. https://doi.org/10.1128/CMR.00027-06.
87. Nimer N, Camp T. Coccidioidomycosis. Pediatr Rev. 2015;36:181–2. https://doi.org/10.1542/pir.36-4-181.
88. Ajello L. Coccidioidomycosis and histoplasmosis. A review of their epidemiology and geographical distribution. Mycopathol Mycol Appl. 1971;45:221–30.
89. Bradsher RW. Histoplasmosis and blastomycosis. Clin Infect Dis. 1996;22(Suppl 2):S102–11.
90. McBride JA, Gauthier GM, Klein BS. Clinical manifestations and treatment of Blastomycosis. Clin Chest Med. 2017;38:435–49. https://doi.org/10.1016/j.ccm.2017.04.006.
91. Anderson EJ, et al. Blastomycosis in children: a study of 14 cases. J Pediatric Infect Dis Soc. 2013;2:386–90. https://doi.org/10.1093/jpids/pis107.
92. Fanella S, et al. Gastric lavage for the diagnosis of pulmonary blastomycosis in pediatric patients. Pediatr Infect Dis J. 2010;29:1146–8. https://doi.org/10.1097/INF.0b013e3181ecc94b.
93. Frost HM, Anderson J, Ivacic L, Meece J. Blastomycosis in children: an analysis of clinical, epidemiologic, and genetic features. J Pediatric Infect Dis Soc. 2017;6:49–56. https://doi.org/10.1093/jpids/piv081.
94. Twarog M, Thompson GR 3rd. Coccidioidomycosis: Recent Updates. Semin Respir Crit Care Med. 2015;36:746–55. https://doi.org/10.1055/s-0035-1562900.
95. Louie L, et al. Influence of host genetics on the severity of coccidioidomycosis. Emerg Infect Dis. 1999;5:672–80. https://doi.org/10.3201/eid0505.990508.
96. Thompson GR 3rd. Pulmonary coccidioidomycosis. Semin Respir Crit Care Med. 2011;32:754–63. https://doi.org/10.1055/s-0031-1295723.
97. Fanella S, Skinner S, Trepman E, Embil JM. Blastomycosis in children and adolescents: a

30-year experience from Manitoba. Med Mycol. 2011;49:627–32. https://doi.org/10.3109/13693786.2010.547994.
98. Laskey WK, Sarosi GA. Blastomycosis in children. Pediatrics. 1980;65:111–4.
99. Wynne JW, Olsen GN. Acute histoplasmosis presenting as the adult respiratory distress syndrome. Chest. 1974;66:158–61.
100. McKinsey DS, McKinsey JP. Pulmonary histoplasmosis. Semin Respir Crit Care Med. 2011;32:735–44. https://doi.org/10.1055/s-0031-1295721.
101. McKinsey DS, McKinsey JP, Brune PR. Diagnosis and management of Histoplasmosis. Curr Fungal Infect Rep. 2008;2:94–102.
102. Jude CM, Nayak NB, Patel MK, Deshmukh M, Batra P. Pulmonary coccidioidomycosis: pictorial review of chest radiographic and CT findings. Radiographics. 2014;34:912–25. https://doi.org/10.1148/rg.344130134.
103. Gabe LM, Malo J, Knox KS. Diagnosis and management of Coccidioidomycosis. Clin Chest Med. 2017;38:417–33. https://doi.org/10.1016/j.ccm.2017.04.005.
104. Merchant M, Romero AO, Libke RD, Joseph J. Pleural effusion in hospitalized patients with Coccidioidomycosis. Respir Med. 2008;102:537–40. https://doi.org/10.1016/j.rmed.2007.11.014.
105. Alkrinawi S, Reed MH, Pasterkamp H. Pulmonary blastomycosis in children: findings on chest radiographs. AJR Am J Roentgenol. 1995;165:651–4. https://doi.org/10.2214/ajr.165.3.7645488.
106. Wheat LJ. Improvements in diagnosis of histoplasmosis. Expert Opin Biol Ther. 2006;6:1207–21. https://doi.org/10.1517/14712598.6.11.1207.
107. Saubolle MA. Laboratory aspects in the diagnosis of coccidioidomycosis. Ann N Y Acad Sci. 2007;1111:301–14. https://doi.org/10.1196/annals.1406.049.
108. Mehta AC, Panchabhai TS, Karnak D. Diseases of the central airways a clinical guide, respiratory medicine. 1 online resource. Springer International Publishing/Imprint/Humana Press. 2016. 385 p. https://www.springer.com/gp/book/9783319298283.
109. Weisel W, Landis FB. Endobronchial lesions in pulmonary blastomycosis. J Thorac Surg. 1953;25:570–81.
110. Failla PJ, Cerise FP, Karam GH, Summer WR. Blastomycosis: pulmonary and pleural manifestations. South Med J. 1995;88:405–10.
111. Sarosi GA, et al. Rapid diagnostic evaluation of bronchial washings in patients with suspected coccidioidomycosis. Semin Respir Infect. 2001;16:238–41.
112. De Schutter I, et al. Microbiology of bronchoalveolar lavage fluid in children with acute nonresponding or recurrent community-acquired pneumonia: identification of nontypeable Haemophilus influenzae as a major pathogen. Clin Infect Dis. 2011;52:1437–44. https://doi.org/10.1093/cid/cir235.
113. Tang LF, Chen ZM. Fiberoptic bronchoscopy in neonatal and pediatric intensive care units: a 5-year experience. Med Princ Pract. 2009;18:305–9. https://doi.org/10.1159/000215729.

Pulmonary Infections in the Immunocompromised Host

20

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Introduction

Pulmonary infections occur frequently in immunocompromised hosts and can be either the presenting symptom of an underlying immunodeficiency or develop secondary to immunosuppressive therapies administered to treat malignancy, rheumatologic disease, or rejection after solid organ transplantation (SOT). The spectrum of pathogens that can affect immunocompromised hosts is broad, including bacteria, fungi, viruses, and parasites, with some pathogens that are significantly less common in hosts with intact immune systems. The host factors that predispose to pulmonary infections in immunocompromised pediatric patients must be appreciated in addition to the understanding that multiple pathogens – bacterial, fungal, and viral – may contribute to disease simultaneously.

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Bacterial Infections

Epidemiology

Bacterial infections remain a significant cause of morbidity and mortality in immunocompromised hosts with pneumonia as a prominent bacterial complication. In some circumstances, recurrent bacterial pneumonia initiates the evaluation for immunodeficiency, such as for primary immunodeficiency (PID) including X-linked hyper-IgM syndrome, chronic granulomatous disease, or hyper-IgE syndrome. Incidence rates range from 31% to 81% in patients with PID, including patients with common variable immunodeficiency (CVID) [1–5]. After hematopoietic stem cell transplantation (HSCT) and SOT, bacterial pneumonia is a common cause of fever and respiratory distress. In serial evaluation of pediatric SOT recipients evaluated for fever in the outpatient setting, 19% of kidney and 24% of heart recipients were diagnosed with bacterial pneumonia [6, 7]. Further, in an earlier study of pulmonary complications in a cohort of pediatric liver transplant recipients, bacterial etiology was identified in more than one-third of events [8]. In a series of 78 allogeneic and 11 autologous HSCT recip-

S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_20

ients, bronchoalveolar lavage (BAL) identified an etiology in 64–68% of HSCT recipients with a bacterial infection as the primary etiology in 52% of allogeneic and 76% of autologous HSCT recipients with a positive BAL [9]. This underscores the utility of BAL in the diagnosis of bacterial pneumonia for this population.

Similar to immunocompetent hosts, pneumococcus is a predominant pathogen; it disproportionately impacts immunocompromised pediatric patients compared to normal hosts. Even in the current era of pneumococcal conjugate vaccination, one study reports pediatric SOT and HSCT at increased risk of invasive pneumococcal infection including pneumonia [10]. Timing of illness occurred later post-transplant for SOT than for HSCT recipients, perhaps related to continued immunosuppression in SOT compared with immune reconstitution and/or revaccination in HSCT. Heart transplant recipients were the most affected SOT group.

Bacterial pathogens recovered from bronchoscopy and BAL in pediatric immunocompromised patients are quite variable. Bacteria typically associated with pneumonia in immunocompetent hosts can be recovered including *Streptococcus pneumoniae* and *Haemophilius influenzae* [11]. However, more recent literature reports that Gram-negative bacteria are the predominant bacterial organisms recovered. An evaluation of BAL results in pediatric patients with PID or cancer demonstrated predominantly Gram-negative organisms including *Pseudomonas spp., Klebsiella spp., Enterobacter spp., Proteus spp., Acinetobacter spp.,* and *Escherichia coli* [12]. Patients with PID had a higher proportion of bacterial pathogens recovered compared to patients with an underlying malignancy. Further, in a contemporary cohort of pediatric immunocompromised patients, Gram-negative bacteria were the most common bacterial pathogens recovered [13]. A cohort of 45 pediatric nonrenal SOT recipients reported five cases of bacterial pneumonia in the early post-transplant period, all of which were secondary to Gram-negative pathogens including *Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Burkholderia cepacia* [14]. The literature describing the resistance profiles of bacterial pathogens in the pediatric immunocompromised host is lacking.

For atypical bacterial pathogens, very little evidence outside of case reports exists in the literature to identify the incidence of these pathogens. One recent study of BAL samples identified no *Mycoplasma pneumoniae* or *Legionella* spp. and only 2.3% were positive for the *Mycobacterium avium* complex [13]. While nontuberculous mycobacterial (NTM) infections are relatively rare in pediatric immunocompromised hosts (~0.3% of pediatric cancer patients) [15], the consequences may be severe. Four patients with disseminated NTM infection involving the lung recovered with therapy, while the two patients with primary pulmonary infections (*Mycobacterium chelonae* and *Mycobacterium abscessus*) expired. Reports indicate that disseminated disease may involve the lungs as illustrated in a case series with four of five patients exhibiting nodular lung disease in conjunction with catheter-associated NTM [16]. Disseminated infections with *Mycobacterium bovis* secondary to BCG vaccination in infants with severe combined immunodeficiency (SCID) often involve the lung, occurring in up to 47% of infants with disseminated disease and second only to skin and lymph node lesions [17]. This may be an important early indicator of underlying severe immunodeficiency in regions where BCG is routinely administered.

In summary, the epidemiology of bacterial pulmonary infections is quite variable, depending on the underlying etiology of immune dysfunction. Identification of pathogens is particularly important in this population, as it can both increase suspicion for a specific immunodeficiency and provide information to target therapy. Further, unlike healthy children, some immunocompromised patients may have multiple pathogens recovered simultaneously due to their depressed host responses.

Diagnostics

Diagnosing pneumonia in immunocompromised hosts requires a multifaceted approach including

diagnostic imaging and microbiological testing. Radiographic findings on chest X-ray or computerized tomography (CT) scan include focal consolidation, ground-glass opacification, and nodular disease. These radiographic features are not pathognomonic for any specific type of bacterial infection in immunocompromised hosts who may have diminished immunologic responses to infection, especially during prolonged neutropenia, for example. Imaging can provide critical information to drive further intervention including empiric therapy, BAL, biopsy, and/or surgery.

Several modalities can be employed in the microbiological diagnosis of bacterial pneumonia although few have been tested specifically in pediatric immunocompromised hosts. In children without comorbidities who are hospitalized with community acquired pneumonia, recent evaluation of blood culture to assist with diagnosis has shown limited value as the rate of bacteremia was low and the pathogens isolated, primarily *Streptococcus pneumoniae*, were highly susceptible in this population [18]. The utility of blood culture in immunocompromised pediatric patients has not been systematically assessed, but may provide additional information to diagnose these complex patients.

Diagnosis for pneumococcal infections has multiple emerging options, which have been evaluated in adults to date. Urinary antigen testing for pneumococcus in adults increases the identification of selected serotypes of pneumococcus beyond traditional use of blood and sputum cultures [19, 20], with newer assays being serotype-specific. Furthermore, quantitative blood PCR and serotype-specific serology have additionally been evaluated with success [20]. In pediatrics, urinary pneumococcal antigen combined with elevated procalcitonin had a diagnostic probability of nearly 80% for community-acquired pneumonia [21]; however, pneumococcal urinary antigen is not currently utilized, and its diagnostic utility in pediatric immunocompromised hosts is untested.

Respiratory samples including sputum, nasopharyngeal swab, tracheal aspirate, and BAL fluid have been used for microbiological diagnosis of pneumonia. In addition to routine aerobic bacterial and mycobacterial cultures along with the use of specialized media such as buffered charcoal yeast extract agar to cultivate *Legionella* species, other methodologies are emerging to identify bacterial pathogens and diagnose pneumonia from these specimens. In children, detection of pathogens by bacterial PCR is decreased by pretest administration of antibiotics, but PCR is less significantly affected (7% reduction) compared to routine bacterial culture (20% reduction) [22]. Furthermore, culture may not be reliable for some atypical pathogens such as *Mycoplasma pneumoniae*, and alternative options using respiratory specimens have included PCR and rapid antigen testing [23, 24]. Bronchoscopic collection of specimens has been further associated with an increased yield compared to other modalities as evidenced by improved *Mycobacterium tuberculosis* recovery from BAL compared to gastric aspirates [25, 26].

Acute Management

Treatment of bacterial pathogens detected from BAL should focus on antibacterial medications that are specific to the pathogen recovered. Often, broad-spectrum empiric antibacterial coverage for both Gram-positive and Gram-negative pathogens based on the previously reported epidemiology of these infections and the local antibiogram is initiated prior to BAL or shortly after BAL due to the urgency in initiating therapy for immunocompromised patients. As culture results are returned, the spectrum of antibiotics can be targeted to treat only the significant pathogens recovered from the BAL. Duration of therapy is highly variable, depending on the pathogen recovered and the underlying diagnosis of the patient including the presence of persistent neutropenia, underlying bronchiolitis obliterans, or uncorrected immunodeficiency. In addition, administration of prolonged courses of antibiotics may be necessary with mycobacterial infections, especially with underlying chronic lung disease, ongoing immunosuppression, or uncorrected PID.

Fungal Infections

Epidemiology

Pulmonary fungal infections (PFI) are major causes of morbidity and death among immunocompromised patients [27, 28]. The incidence of PFI among children has increased over the past years, mainly due to the rapidly growing number and diversity of pediatric SOT and HSCT recipients along with increasing use of immunosuppressive medications [29, 30]. This population is characterized by high susceptibility to PFI and higher mortality rates [30, 31]. Organ-specific data on invasive fungal diseases in pediatric patients have been limited. However, incidence rates among pediatric patients appear to be lower than in adults. The most important fungal infections of the lung in immunocompromised children are aspergillosis, *Pneumocystis jirovecii,* mucormycosis, cryptococcosis, and histoplasmosis. Other environmental molds such as *Fusarium and Scedosporium* have been increasingly recognized as pathogens in immunocompromised hosts with pulmonary disease.

Pulmonary aspergillosis is relatively common in immunocompromised patients. Transplant patients are particularly susceptible to invasive aspergillosis, which includes pulmonary involvement in 85–100% of patients [32, 33]. Prevalence of invasive aspergillosis (IA) varies depending on transplant type, with recent estimates at 8.3% (lung), 7.1% (heart), 2.7% (HSCT), 2.6% (multiorgan), 1.3% (kidney), and 1.2% (liver) [32, 33].

Prior to routine prophylaxis, *Pneumocystis jirovecii* pneumonia (PJP) occurred in 5–15% of HSCT and SOT patients [34–37]. The widespread use of TMP-SMX prophylaxis has drastically reduced this incidence to 1–2.5%, but mortality still remains as high as 70% [38–40].

Pneumonia due to *Mucorales* is rare and mainly occurs in immunocompromised hosts, but it can be associated with 50–80% of the mortality [41–43]. The incidence of mucormycosis has increased over the last decade [44]. In prospective studies from the American Transplant-Associated Infection Surveillance Network (TRANSNET), mucormycosis was the third leading cause of invasive fungal diseases (8% of cases) among HSCT recipients and the sixth leading cause (2% of cases) among SOT patients and 53% of all cases had pulmonary disease [45–47]. Pulmonary disease is common in mucormycosis, occurring in 33–53% of cases in patients with underlying hematologic malignancy in other studies from Europe, North America, and France [41].

Pulmonary disease due to other fungi including *Cryptococcus, Fusarium, Candida* spp, endemic mycoses such as *Histoplasma, Coccidioides, Blastomyces*, and other environmental fungi such as *Scedosporium, Fusarium,* and *Alternaria* have been reported but are less common. Cryptococcosis, while common in adults, is uncommon in children. Candidemia is relatively common in immunocompromised patients in all age groups and hematogenous seeding of the lungs and pulmonary disease can occur, but is infrequent. Isolation of *Candida* species in sputum generally does not indicate pulmonary disease and should not lead to targeted therapy. Pneumonia due to *Fusarium* or *Scedosporium* should be considered among patients with failure to respond to therapy as they have unique susceptibility patterns.

Aspergillus *Aspergillus* spp. is the most common cause of PFI in immunocompromised children. Among SOT recipients, pulmonary aspergillosis is more common during the second to the sixth month following transplantation, whereas HSCT recipients are at high risk during neutropenia before and after transplantation. Graft-versus-host disease (GVHD), neutropenia, corticosteroid use, and nearby construction at the time of transplantation are commonly reported risk factors. Overall mortality can be as high as 90% with a median survival of 23 days (2–90) [32]. Common clinical presentations of pulmonary aspergillosis comprise acute IA, chronic

pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, chronic cavitary aspergillosis, and aspergilloma. The genus *Aspergillus* includes almost 200 species, but up to 90% of the cases are caused by *A. fumigatus*, followed by *A. flavus, A. niger*, and *A. terreus*. Aspergillus conidia (asexual spores) are ubiquitous in the environment [48]. Following inhalation of airborne spores and deposition of conidia in the alveoli of the immunocompromised host, angioinvasion leads to dissemination to other organs such as eyes, brain, and skin.

Clinical manifestations of acute invasive pulmonary aspergillosis are nonspecific. Persistent fever in the setting of broad-spectrum antimicrobial therapy is the most commonly reported finding and can be associated with nonproductive cough, hemoptysis, or chest pain. Clinical course can be rapid, and hypoxemia and dyspnea may develop within 1–2 days. Radiographic signs of aspergillosis are also nonspecific and can vary, including single or multiple nodular or cavitary lesions, larger masses, or diffuse bilateral pulmonary infiltrates [49, 50]. In up to 30% of the patients with IA, chest X-ray can be normal. In the early stages of aspergillosis, classic findings on CT may include the "halo" sign (11% of children), a rim of ground-glass opacity that surrounds a nodule, and the "air crescent" sign (2.2% of children), a cavitated lesion with an intracavitary mass, and a surrounding rim of air [50, 51].

Timely diagnosis and prompt initiation of antifungal therapy or surgery if indicated is the key to successful outcome in all IA infections [33, 51, 52] . Despite the advances in the field, the tools available for the diagnosis of IA continue to lack high sensitivity and specificity. The European and US guidelines group IA into proven, probable, and possible based on the host factors, clinical and radiological findings, and mycological evidence [53, 54]. Definitive diagnosis of aspergillosis requires isolation of the mold in culture and identification of the hyphae on histopathology. However, blood cultures and cultures of sputum or BAL fluid are reported to have low sensitivity. Non-culture-dependent methods such as the detection of the antigens from the fungal cell wall in the blood or BAL and PCR-based methods have been developed over the last decades and have been increasingly used in clinical practice. These methods include galactomannan (GM) assay, 1,3-beta-D-glucan (BDG) assay, and lateral flow device, which are summarized in Table 20.1. GM is a polysaccharide present in the cell wall of *Aspergillus* spp with optimal sensitivity and specificity when tested on BAL fluid. Serum levels of GM can be trended over time and appear to be closely related to the dynamics of angioinvasion and may correlate with patient outcome [55–57]. Twice-weekly GM testing leads to the highest specificity, which can be up to 98%. BAL GM positivity also has been reported to anticipate the culture positivity and the onset of the symptoms among HSCT patients. However, there are important caveats to be considered when using GM EIA for diagnosis of invasive pulmonary aspergillosis (Table 20.1). The technique used for BAL, such as the volume of instilled saline or type of collected BAL fluid (i.e., alveolar or bronchial), can impact the performance of GM testing in BAL fluid. Another polysaccharide that is present in the cell wall of *Aspergillus* spp. is 1,3-beta-D-glucan (BDG) and there are commercially available assays to measure serum levels (e.g., Fungitell®, Associates of Cape Cod, Inc., MA, USA). A serum level of >= 80 pg/mL is interpreted as positive [58], and can occur with a variety of fungal pathogens, including *Candida*, *Fusarium*, and *Pneumocystis*. Another recently developed point-of-care diagnostic tool for detection of IA is a lateral flow device that uses *Aspergillus*-specific monoclonal antibody, and can be highly specific to detect a mannoprotein produced by actively growing *Aspergillus* species. It has been tested in blood and BAL fluid specimens, showing promising results in patients with cancer, SOT, and lung disease, but further studies are needed to determine the clinical usefulness of this new test. PCR-based

Table 20.1 Nonculture, nonmolecular tests used for the diagnosis of invasive Aspergillosis[a]

	Galactomannan	1,3 β-D-glucan	Lateral flow device
FDA approval	Serum, BAL	Serum	Not approved
Sensitivity	Serum: 41–78% BAL: 87% (79–92%)	77% (67–84%)	Serum: 20–68% BAL: 80–100%
Specificity	Serum: 60–95% BAL: 89% (85–92%)	85% (80–90%)	Serum: 72–98% BAL: 81–95%
Clinical significance	Used for early detection of invasive aspergillosis Nonspecific for *Aspergillus species*	Nonspecific for *Aspergillus species*	Potential use as point-of-care testing Nonspecific for *Aspergillus species*
False-negative results	Concomitant use of antifungal prophylaxis or therapy	Concomitant use of antifungal prophylaxis or therapy	Not reported
False-positive results	Semisynthetic β-lactam antibiotics (e.g., iv pip/taz or amox/clav) Infections with *Fusarium* spp, *Penicillium* spp and *Histoplasma capsulatum*. Severe gastrointestinal tract mucositis or graft-versus-host disease Contamination of foods with Aspergillus or closely related fungi, such as *Penicillium* spp. Blood products collected in Fresenius Kabi, Germany bags Intravenous immunoglobulin	Semi-synthetic β-lactam antibiotics (e.g., iv pip/taz or amox/clav) Exposure to cellulose membranes via hemodialysis/ hemofiltration or filtered blood or blood-derived products Blood stream infections with bacteria (e.g., *Pseudomonas aeruginosa*) Exposure to gauze Intravenous immunoglobulin Albumin infusion	Doxycycline

BAL Bronchoalveolar lavage, *pip/taz* piperacillin- tazobactam, *amox/clav* amoxicillin-clavulanate, *iv* intravenous
[a]Modified from Miceli et al.

methods that can be applied to blood, BAL fluid, and tissue have been reported to have high sensitivity for detection of IA. However, the usefulness of these new methods in clinical practice remains under investigation. Having at least two positive PCR tests increases specificity to 95%, with a sensitivity of 64% for IA [59]. Another approach to optimize the performance of diagnostic methods used for invasive pulmonary aspergillosis can be a combination of different assays for high-risk patients. In a recent study, the combination of GM EIA with either PCR or lateral flow was shown to increase the sensitivity to 94–100% without compromising specificity [60].

Pneumocystis jirovecii *Pneumocystis jirovecii* is a ubiquitous pathogen and can cause asymptomatic infection that can progress into life-threatening disease in immunocompromised hosts. *Pneumocystis jirovecii* pneumonia (PJP) continues to be one of the most frequent and severe opportunistic infections among individuals with HIV/AIDS, but patients with hematologic malignancies, transplant recipients, patients on glucocorticoid therapy, and patients with defects in cell-mediated immunity are also at risk.

Pneumocystis can be transmitted through person-to-person spread by respiratory droplets. Patients can present with fulminant respiratory failure associated with fever, dry cough, and shortness of breath. Hypoxemia at rest or with exertion or increased alveolar-arterial oxygen tension gradient is seen in almost all patients with PJP. The typical radiographic signs of PJP are

diffuse, bilateral, interstitial infiltrates that can coalesce to form a ground-glass appearance. High-resolution CT provides enhanced sensitivity relative to chest X-ray [61]. An elevated lactate dehydrogenase (LDH) has been reported to be a clinical indicator of possible PJP in HIV-infected individuals. However, among non-HIV patients, its utility is limited due to low specificity in the setting of underlying hematologic malignancy or other causes of acute lung injury. BDG, similar to *Aspergillus* spp., is a cell wall component of *Pneumocystis* and has been proposed as a serologic biomarker for PJP diagnosis [62]. Although nonspecific, when elevated in a patient with risk factors and clinical findings suggestive of PJP, further microbiologic or molecular diagnosis should be pursued to rule out PJP. Since *Pneumocystis* cannot be cultured, the definitive diagnosis of PJP requires identification of the organism by dye-based staining, fluorescent antibody staining, or PCR-based assays on induced sputum or BAL fluid. In a retrospective multicenter study including 55 adult patient without HIV/AIDS, BAL was the diagnostic in 98%, induced sputum in 50%, and lung biopsy in 38% of the patients [63]. PCR provides enhanced sensitivity and may be useful for samples with negative stains [64].

Cryptococcus *Cryptococcus neoformans* is a ubiquitous encapsulated yeast found in soil in areas frequented by birds such as pigeons and chickens. The cryptococcus genus comprises more than 70 species, but the two main pathogenic species are *C. neoformans* and *C. gattii*. The most common route of acquisition is inhalation. The majority of clinical cases are caused by reactivation of latent infection [65]. Individuals with HIV/AIDS, prolonged treatment with glucocorticoids, SOT/HSCT recipients, children with primary immunodeficiencies such as hyper-immunoglobulin M syndrome or SCID, and those with liver disease and sarcoidosis are at high risk. Despite the advances in treatment of HIV, cryptococcosis continues to be reported in up to 30% of the AIDS patients in some studies. Donor-derived cryptococcosis should be considered for cases identified within the first month following transplant, especially if there is more than one affected recipient from a single donor [66].

Pulmonary disease is the second most common presentation of cryptococcosis. However, diagnosis may be problematic because of the lack of specificity of the symptoms. Clinical manifestations due to pulmonary cryptococcosis can range from asymptomatic pneumonia to acute respiratory failure. Symptoms are typically nonspecific, including fever, chest pain, dyspnea, and cough. In a retrospective study that included 34 immunocompromised patients with cryptococcal pneumonia, 84% presented with concomitant pulmonary and meningeal infections [67]. Radiological features of pulmonary cryptococcosis can vary but commonly include solitary or few well-defined, noncalcified nodules. These nodules are often pleural based and may be cavitary. The right lower lobe is the most common location and multiple nodules are reported in >60% of patients [68]. The serum cryptococcal antigen is an excellent screening tool and is positive in ~80% of patients with isolated pulmonary disease and in ~97% of patients with CNS disease or disseminated cryptococcosis [66, 69]. Isolation of cryptococcus from respiratory samples can represent a true pathogen in immunocompromised patients, but also may be due to colonization. Histology can help to identify active infection based on demonstration of encapsulated yeast forms in sputum, BAL, or tissue specimens. All immunocompromised patients with pulmonary cryptococcosis should have blood and cerebrospinal fluid (CSF) cultures as well as blood and CSF cryptococcal antigen testing to evaluate for disseminated disease regardless of symptoms [66].

Viral Infections

Epidemiology

Viral infections within the respiratory system are common in all children, but they can have more

severe and prolonged consequences in the immunocompromised host. While these infections will resolve without treatment in most children, immunocompromised children often require more intensive supportive care and may necessitate use of antivirals. Respiratory viral infections (RVI) such as influenza and respiratory syncytial virus (RSV) are an important cause of morbidity and mortality in pediatric immunocompromised hosts. A recent retrospective analysis demonstrated that pediatric patients developed an RVI associated with hospitalization in the 12 months following transplantation in 14.5% of SOTs [70] and 16.6% of HSCTs [71]. In SOT patients, this study did not identify any attributable mortality, but 51% of patients required respiratory support and 6% had significant pulmonary sequelae [70]. Among HSCT patients, there was a 5.4% attributable case-fatality rate, 48% required respiratory support, and 14% developed significant pulmonary sequelae [71]. Severe viral infections can also occur in patients with other forms of immunocompromise, particularly T- or B-cell defects (e.g., SCID, X-linked agammaglobulinemia, HIV), although these often present as disseminated disease rather than isolated pulmonary disease. Severe viral infections have also been described in children on biologic response inhibitors such as rituximab or tofacitinib (a JAK/STAT inhibitor) [72]. Due to their high prevalence and significant potential for morbidity and mortality, it is important to consider viral infections on the differential of any immunocompromised child with a pulmonary infection.

Herpesviruses

Herpesviridae is a large family of double-stranded DNA viruses that all result in latent, lifelong infection within the host. These viruses primarily establish latency within monocytes (cytomegalovirus, CMV), neurons (varicella zoster virus, VZV, and herpes simplex virus, HSV), or lymphocytes (Epstein–Barr virus, EBV, or human herpesvirus 6, 7, or 8, HHV-6, -7, and -8). Herpesvirus infection is predominantly controlled by cell-mediated immunity, leading to a high risk of CMV disease in children with compromised cell-mediated immunity (i.e., HIV, SCID, HSCT, and SOT recipients). Disease can be caused by primary infection or reactivation from latency. Many of these viruses have a high prevalence in the population, making positive tests more difficult to interpret. Due to persistent latency, a patient may have evidence of infection based on serum or BAL studies but this does not always correlate with causation of the active disease process. Positive staining in lung biopsy samples is typically indicative of herpesvirus disease, but biopsy is often considered too risky. Therefore, while it is important to consider and treat herpesvirus infections within the lung of the immunocompromised host, coinfection with other pathogens is common and should be evaluated for.

Cytomegalovirus CMV is a ubiquitous virus, with an estimated seroprevalence of about 50% in the United States [73]. Risk for disease in pediatric transplant recipients has substantially decreased since the advent of preventative strategies, although morbidity and mortality persist, particularly in pediatric lung transplant recipients. In a retrospective review of pediatric lung transplant recipients, nearly 18% of patients developed CMV disease in the 12 months following transplantation and CMV infection was associated with an increased mortality risk [74].

Clinical manifestations of CMV disease in immunocompromised children are variable but typically include cough, increased respiratory effort, and diffuse abnormal breath sounds [75]. Fever is only present in 40–70% of patients [75, 76]. Around 30–50% of children develop respiratory failure requiring mechanical ventilation, and mortality was 13% in one study [75, 76]. Imaging findings are typically diffuse haziness, often with ground-glass opacities seen on CT scan [75]. As with all herpesviruses, diagnosis can be challenging and it is often unclear whether CMV is the definitive cause of disease. CMV infection can be

detected in a variety of ways. CMV PCR is readily available and can be used to assess CMV burden in blood, BAL fluid, or tissue specimens. CMV culture from BAL has also been used, although many laboratories are moving toward PCR testing only. CMV serology is frequently not helpful for diagnosis in immunocompromised patients, although a positive CMV IgM in a previously seronegative patient would be suggestive of a new CMV infection. The gold standard for diagnosis is histopathology that demonstrates inclusion bodies in lung tissue. There have been multiple recent studies to determine the specificity of positive CMV testing from BAL specimens in children. One study found that the vast majority of children with a positive CMV from BAL did not have correlative CMV pulmonary disease [76]. However, patients with very high viral loads in BAL fluid appear to be more likely to have CMV disease [77–79].

Varicella Zoster Virus Infection with VZV can result in severe complications in the immunocompromised host, including pneumonia. With the introduction of VZV vaccination in 1995, overall incidence of disease has decreased by more than 95% [80]. However, although the incidence has not been clearly defined, disease can occur from the vaccine strain itself in immunocompromised hosts and exposure to the vaccine should be considered when assessing risk. Pulmonary manifestations of VZV are typically a complication of disseminated infection. VZV pneumonia is a relatively common complication in adult immunocompromised hosts, but appears to occur less frequently in children. A recent study estimated the prevalence of VZV pneumonia as 8% of immunocompetent children hospitalized for varicella infection [81]. Prevalence in immunocompromised children remains unclear.

Clinically, patients will typically present first with fever and rash, which may be a nonspecific diffuse maculopapular rash or the classic vesicular rash associated with varicella. Then, over the next 3–5 days, patients will become more ill and develop respiratory distress with hypoxia [81]. Respiratory failure can occur and noninvasive or invasive mechanical ventilation is frequently needed [82]. Imaging findings are variable but typically include bilateral interstitial markings that may appear nodular on CT [81, 82]. Diagnosis can be made by VZV PCR in blood, which is expected to be positive in all patients with VZV pneumonia [82]. Significance of VZV PCR from BAL fluid is unclear. Positive VZV staining or PCR from lung biopsy would be highly suggestive of VZV pneumonia. VZV pneumonia has an associated high mortality rate and should be promptly treated when suspected.

Herpes Simplex Virus Due to the use of routine acyclovir or valganciclovir prophylaxis and a predilection of the virus for the squamous epithelium and neurons, respiratory complications from HSV infection are rare [83]. However, HSV pneumonia or tracheobronchitis can occur secondary to disseminated HSV disease or following direct spread from vesicles through the oropharynx. Clinical presentation of HSV pneumonia is not clearly described in children, but in adults, it typically includes respiratory distress, hypoxemia, and low-grade fevers [84]. Patients may develop Acute respiratory distress syndrome (ARDS) and acute respiratory failure that does not improve on standard therapy and leads to prolonged ventilation [84]. Imaging findings are variable and chest X-ray may be normal. When abnormalities are present, HSV typically results in diffuse bilateral symmetric infiltrates with ground-glass opacities on CT [83, 85]. Although less common, patients may instead have bilateral asymmetric peribronchial airspace consolidations [83, 85]. Laboratory findings are generally nonspecific, although patients with HSV pneumonia may have a notable leukocytosis [84]. Similar to the other herpesviruses, definitive diagnosis can only be made by pathology of lung tissue or of BAL cytology. For HSV, the pathognomonic finding is intranuclear inclusion bodies [84]. HSV cultures, PCR, or immunoglobulins are difficult to interpret because of

the high prevalence of carriage and asymptomatic oral shedding.

Epstein–Barr Virus EBV is a ubiquitous virus, infecting more than 90% of the adult population. The most concerning manifestation of EBV infection in immunocompromised patients is oncologic. EBV is associated with post-transplant lymphoproliferative disorders (PTLD) in patients that have received HSCT or SOT. It is also associated with lymphomas in HIV-positive patients. Because of risk for PTLD, EBV status in donor and recipient is determined prior to transplantation and EBV is closely monitored for after transplantation. EBV-positive PTLD can present within the thoracic cavity as pulmonary parenchymal disease, extraparenchymal erosions, or less commonly as an interstitial pneumonia [86, 87]. EBV pulmonary disease in immunocompromised patients is typically a manifestation of PTLD, but in rare cases, EBV pneumonia without PTLD can occur [88–90].

Patients with pulmonary PTLD will often present clinically with extrapulmonary manifestations such as fever and lymphadenopathy [91]. Pulmonary symptoms are often mild initially, including cough and shortness of breath, but can progress over 1–2 weeks to respiratory failure, multiorgan failure, and death [90, 91]. Imaging findings with EBV-associated pneumonia are variable and may be negative. The most common imaging appearance is multifocal patchy and diffuse ground-glass changes [91]. CT findings of diffuse lung infiltration with mediastinal lymphadenopathy and hepatosplenomegaly would be highly suggestive of PTLD [87, 91, 92]. When EBV disease is being considered, pathologic diagnosis is essential due to the risk of PTLD. Pathology samples from a patient with PTLD demonstrate a wide range of findings from plasmacytic hyperplasia to classical Hodgkin lymphoma [93]. Pathologic staining that is positive for EBER (EBV RNA) and/or LMP-1 (EBV protein) is indicative of EBV infection [91]. Other EBV testing yields variable results and can be challenging to interpret, as for all herpesviruses [94]. Options for EBV testing include serology, with EBV IgM being indicative of acute primary infection or reactivation, and EBV PCR from the blood or from BAL fluid, which may be positive in the absence of EBV disease [90, 94].

Other Herpesviruses The remaining herpesviruses, HHV-6A, HHV-6B, HHV-7, and HHV-8, have each been associated with pulmonary disease in immunocompromised patients, although the occurrence of pulmonary disease is exceptionally rare [95]. These viruses predominantly cause disease in HSCT patients and HIV patients due to their profound defects in cell-mediated immunity. However, positive findings should always be interpreted with caution, as these are ubiquitous viruses that may be present without causing disease.

HHV-6 and HHV-7 are overall very similar to the other herpesviruses described above. Clinical presentation of HHV-6 or -7 pneumonia typically includes fever, cough, and respiratory distress that progresses to respiratory failure [96–98]. Imaging findings appear to be predominantly bilateral diffuse ground-glass opacities on CT scan [96, 99, 100]. Similar to all other herpesviruses, these viruses are abundant in the population and may be present in low quantities in blood, BAL fluid, or tissue without causing disease. Presence in diseased lung tissue on biopsy or high viral copy number in BAL fluid is more suggestive of these viruses being the etiologic agent.

HHV-8 or Kaposi sarcoma-associated herpesvirus (KSHV) has unique pulmonary manifestations related to its oncogenic properties. These manifestations are predominantly described in adult HIV patients, where KSHV can cause pulmonary Kaposi's sarcoma (KS), primary effusion lymphoma, and pulmonary multicentric Castleman's disease [101–104]. Disease patterns due to HHV-8 in pediatric immunocompromised patients are unclear. However, KS can occur in pediatric HIV patients, particularly in sub-Saharan Africa, and has been described in increasing frequency in pediatric transplant recipients [105]. Pulmonary KS can present clini-

cally with shortness of breath, chest pain, hemoptysis, weight loss, and low-grade fever [101, 105]. Imaging typically demonstrates diffuse bilateral nodularity and extensive lymphadenopathy and may also have areas of focal nodular consolidation [101, 106]. Diagnosis requires bronchoscopy to evaluate for violaceous or bright red maculopapular lesions on the lower airways, which are pathognomonic [101]. Additional pathologic confirmation of the diagnosis is also helpful when feasible.

Respiratory Viruses

Pulmonary disease due to respiratory viruses such as influenza, RSV, adenovirus, rhinovirus, human metapneumovirus (hMPV), parainfluenza virus, and coronavirus are very common, particularly in the winter months. Immunocompromised children are more likely to develop severe infections from respiratory viruses and have a higher associated morbidity and mortality. Respiratory viruses generally present similarly with initial rhinorrhea and/or cough, which may progress over time to respiratory distress and respiratory failure. Fever is often absent, with fever being most likely in influenza, RSV, and adenovirus infections [107–111]. Imaging may be normal or there may be diffuse bilateral consolidations, often with ground-glass opacities on CT [108, 112]. Diagnosis is typically through single or multiplex PCR, which can be performed on upper respiratory tract specimens (nasopharyngeal swab or wash), BAL, or lung biopsy tissue. Detection in the lower respiratory tract is associated with a worse outcome. Unlike herpesviruses, a positive test for one or more of these viruses is generally indicative of that virus as contributing to disease pathogenesis, particularly for influenza or adenovirus. There are circumstances in which prolonged viral shedding can occur in immunocompromised patients so positive tests should be interpreted in the setting of symptom history and previous test results. Consultation with an infectious disease specialist should be considered to determine if treatment is indicated in this setting. With all respiratory viruses, coinfection with other pathogens or superimposed bacterial pneumonia is common. Therefore, each contributing pathogen should be considered and managed as indicated.

Influenza The global burden of influenza infection is high, with an estimated 9.2–35.6 million infected and 12,000–56,000 deaths annually in the United States [113]. Among immunocompromised children, the significance of these infections is greater, with a much higher morbidity and mortality rate [110]. For example, in two recent studies of pediatric HSCT patients, 10–25% required mechanical ventilation [71, 114]. Classically, clinical presentation includes high fever, chills, headache, dry cough, myalgia, malaise, and anorexia [109]. Influenza infection can be much subtler in immunocompromised patients, presenting with only cough, fever, or malaise [109, 110]. Chest X-ray will likely demonstrate diffuse bilateral infiltrates, which may appear patchier or more consolidated than with other viral pneumonias.

Respiratory Syncytial Virus RSV infections are prevalent in children, particularly in the winter months. Immunocompromised patients, especially those with HSCT, SCID, or hematologic malignancies, have a much higher morbidity and mortality associated with RSV infection. Severe RSV infection has been well described in HSCT patients, where it is a common cause of lower respiratory disease, but RSV can cause clinically significant disease in any immunocompromised patient [108]. A number of factors have been identified to specifically increase the risk for severe RSV infection. These include lymphopenia, young age (≤2 years), total body irradiation, and high dose steroids [108, 115, 116].

Many immunocompromised patients with RSV progress to severe respiratory distress and failure, with 57% of HSCT patients requiring respiratory support and 18% of HSCT patients requiring mechanical ventilation [71]. Unlike in

immunocompetent patients, those immunocompromised patients that develop moderate-to-severe disease are typically treated with antiviral therapy.

Adenovirus Adenovirus infection is common in immunocompromised patients, although prevalence in pediatric patients is not well described. Acquisition may be *de novo* or from reactivation of latent virus. Adenovirus causes a wide variety of manifestations, including upper and lower respiratory tract disease, keratoconjunctivitis, hemorrhagic cystitis, and gastroenteritis. Immunocompromised patients have a much higher risk of developing multiorgan disease and severe disseminated disease. Disseminated disease with multiorgan failure in immunocompromised children carries a mortality rate of over 80% [117]. Patients with disseminated disease typically have severe pulmonary manifestations [117, 118]. In a recent study of pediatric allogeneic HSCT patients, 12.3% of patients developed adenovirus infection and this was associated with a significantly greater mortality risk [119].

In addition to adenovirus PCR testing from respiratory specimens, quantitative PCR of the blood may also be beneficial, particularly in monitoring treatment response. Lung biopsy may demonstrate necrotizing bronchitis, bronchiolitis, mononuclear cell infiltration, and hyaline membranes [111]. Because of the high risk for severe complications and disseminated disease, antiviral therapy is routinely used to treat adenovirus infection in immunocompromised hosts.

Other Respiratory Viruses In addition to the viruses discussed above, all of the other respiratory viruses that infect immunocompetent children can also cause more severe disease in the setting of immunocompromise. The most common of these are rhinovirus, hMPV, parainfluenza virus, and coronavirus. These viruses typically present as upper respiratory tract disease, although all can cause lower respiratory tract disease manifesting as pneumonia. Of these viruses, hMPV has been identified as the most likely to cause lower respiratory tract disease in immunocompromised children [71]. hMPV is also the most likely to have associated fever and has the highest all-cause case-fatality rate of pediatric HSCT patients [71]. In general, infection with these viruses tends to have less severe consequences than with influenza, RSV, and adenovirus, but respiratory failure and death have been described.

Parasitic Infections

Parasitic infections of the lung appear to be relatively rare in pediatric immunocompromised patients with mostly case reports in the literature [120]. Some infections may be life threatening such as *Strongyloides* hyperinfection syndrome, which may present with Gram-negative sepsis. Additionally, parasitic infections may be donor-derived in the case of solid organ transplantation, although this is a rare event [121]. These infections primarily involve the intestinal tract, but the life cycle for some parasites including *Ascaris* and *Strongyloides* involve migration through the lung where they may be diagnosed on evaluation by BAL with direct observation [122]. However, diagnostic methodology for these parasitic pathogens consists primarily of serologic measurement and direct observation of larvae/oocytes in a standard stool specimen [123]. Additional testing of stool by PCR for *Strongyloides stercoralis* may increase recovery in transplant recipients [124].

Summary

Pulmonary infections are common complications in immunocompromised children, particularly HSCT, SOT, and PID patients. These

infections may be due to common pathogens seen in all children (e.g., *S. pneumoniae*, *H. influenzae*, and respiratory viruses) or pathogens that do not cause significant disease in immunocompetent hosts (e.g., Legionella, *Aspergillus*, PJP, *Mucormycosis,* and herpesviruses) and are summarized in Table 20.2. In the setting of immune compromise, patients have a much higher risk of morbidity and mortality due to pulmonary disease, so pathogen identification and early intervention are critical. Clinical symptoms and imaging findings are less predictable in immunocompromised patients and may not facilitate diagnosis. Therefore, diagnosis often requires consideration of their current immune status, an extensive exposure history, and invasive studies such as BAL or biopsy. Additionally, immunocompromised patients will often have multiple pathogens contributing to disease. Identifying all pathogens is important, as even the most viral infections require therapy in this population.

Table 20.2 Overview of major pulmonary infections in an immunocompromised host

	Population at highest risk	Common imaging findings	Diagnostic test (sample type)	Treatment	Prevention
S. pneumoniae	HSCT, SOT, PID	Focal consolidation	Culture (BAL, biopsy)	Ampicillin, cephalosporins	Vaccine (PCV13 and PPSV23)
H. influenzae	↓	↓	↓	Cephalosporins	Vaccine
Gram negatives				4th generation cephalosporins	None
Mycoplasma	HSCT, Cancer, SCID	Diffuse patchy infiltrates	PCR (Nasopharyngeal, BAL, biopsy)	Azithromycin	None
Legionella	↓	↓	Antigen test, culture on chocolate agar (BAL, biopsy)	Azithromycin, levofloxacin	None
NTM			Culture, PCR (BAL, biopsy)	Triple therapy	None
Aspergillus	HSCT, SOT, PID	Nodules, cavitary lesion(s)	Culture (BAL, biopsy); Galactomannan (serum, BAL); 1,3-β-D-glucan (serum); PCR (blood, BAL, tissue)	Voriconazole (first-line), Amphotericin B, posaconazole	Antifungal prophylaxis
PJP	HSCT, SOT, HIV/AIDS, PID	Diffuse ground-glass opacities	Stain (sputum, BAL, biopsy), PCR	TMP-SMX	TMP-SMX prophylaxis
Mucormycosis	HSCT and SOT	Cavitary lesion(s)	Culture (BAL often nondiagnostic, biopsy preferred)	Amphotericin B, posaconazole	None
Cryptococcus	HSCT, SOT, HIV/AIDS, SCID	Nodules	Culture (BAL, biopsy), cryptococcal antigen (serum)	Fluconazole, Amphotericin B + 5-FC if severe disease	Antifungal prophylaxis
CMV	HSCT, SOT, SCID, HIV/AIDS	Bilateral haziness, ground-glass opacities	PCR (blood, BAL, biopsy), histology	Ganciclovir	Pretransplant screening, (val) ganciclovir

(continued)

Table 20.2 (continued)

	Population at highest risk	Common imaging findings	Diagnostic test (sample type)	Treatment	Prevention
VZV		Bilateral interstitial findings, nodules		Acyclovir	Vaccine
HSV		Bilateral haziness, ground-glass opacities		Acyclovir	Prophylaxis
EBV		Bilateral haziness +/− LAD[a]		Rituximab, chemotherapy	Pretransplant screening
HHV-6 and HHV-7		Bilateral ground-glass opacities		Ganciclovir, cidofovir, foscarnet	None
KSHV		Pulmonary KS – bilateral nodules, diffuse LAD	Visualize lesions on bronchoscopy, histology of biopsy	Cidofovir, chemotherapy	None
Influenza		Diffuse bilateral infiltrates	PCR (nasopharyngeal samples, BAL, biopsy)	Oseltamavir	Vaccine
RSV				Ribavirin, IVIG	Palivizumab[a]
Adenovirus				Cidofovir	None

Abbreviations: *HSCT* hematopoietic stem cell transplantation, *SOT* solid organ transplantation, *PID* primary immunodeficiency, *BAL* Bronchoalveolar lavage, *PCV13* 13-valent pneumococcal conjugated vaccine, *PPSV23* 23-valent pneumococcal polysaccharide vaccine, *SCID* severe combined immunodeficiency, *NTM* non-tuberculous mycobacteria, *PJP Pneumocystis jirovecii* pneumonia, *CMV* cytomegalovirus, *VZV* varicella-zoster virus, *HSV* Herpes simplex virus, *HHV* Human herpes virus, *EBV* Epstein–Barr Virus, *KSHV* Kaposi's Sarcoma-associated Herpesvirus, *RSV* respiratory syncytial virus, *LAD* lymphadenopathy

[a]Palivizumab prophylaxis is reserved only for very high-risk patients (severely immunocompromised children who are ≤24 months at the start of RSV season)

References

1. Gathmann B, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014;134(1):116–26.
2. Yazdani R, et al. Infectious and noninfectious pulmonary complications in patients with primary immunodeficiency disorders. J Investig Allergol Clin Immunol. 2017;27(4):213–24.
3. Winkelstein JA, et al. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore). 2003;82(6):373–84.
4. Hanson EP, et al. Hypomorphic nuclear factor-kappaB essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. J Allergy Clin Immunol. 2008;122(6):1169–1177 e16.
5. Sullivan KE, et al. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr. 1994;125(6 Pt 1):876–85.
6. Yin S, Powell EC, Trainor JL. Serious bacterial infections in febrile outpatient pediatric kidney transplant recipients. Pediatr Infect Dis J. 2011;30(2):136–40.
7. Yin S, Trainor JL, Powell EC. Serious bacterial infections in febrile outpatient pediatric heart transplant recipients. Acad Emerg Med. 2009;16(10):942–8.
8. Mack CL, et al. Pulmonary complications following liver transplantation in pediatric patients. Pediatr Transplant. 2000;4(1):39–44.
9. Kasow KA, et al. Diagnostic yield of bronchoalveolar lavage is low in allogeneic hematopoietic stem cell recipients receiving immunosuppressive therapy or with acute graft-versus-host disease: the St. Jude experience, 1990-2002. Biol Blood Marrow Transplant. 2007;13(7):831–7.
10. Olarte L, et al. Invasive pneumococcal infections in children following transplantation in the pneumococcal conjugate vaccine era. Transpl Infect Dis. 2017;19(1).
11. Ben-Ari J, et al. Yield of bronchoalveolar lavage in ventilated and non-ventilated children after bone

marrow transplantation. Bone Marrow Transplant. 2001;27(2):191–4.
12. Efrati O, et al. Fiberoptic bronchoscopy and bronchoalveolar lavage for the evaluation of pulmonary disease in children with primary immunodeficiency and cancer. Pediatr Blood Cancer. 2007;48(3):324–9.
13. Nadimpalli S, et al. Diagnostic yield of bronchoalveolar lavage in immunocompromised children with malignant and non-malignant disorders. Pediatr Pulmonol. 2017;52(6):820–6.
14. Wiesmayr S, et al. Experience with the use of piperacillin-tazobactam in pediatric non-renal solid organ transplantation. Pediatr Transplant. 2007;11(1):38–48.
15. Apiwattankul N, et al. Infections caused by rapidly growing mycobacteria spp in children and adolescents with cancer. J Pediatr Infect Dis Soc. 2015;4(2):104–13.
16. Wei MC, et al. Nontuberculous mycobacteria infections in immunocompromised patients: single institution experience. J Pediatr Hematol Oncol. 2009;31(8):556–60.
17. Marciano BE, et al. BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies. J Allergy Clin Immunol. 2014;133(4):1134–41.
18. Neuman MI, et al. Utility of blood culture among children hospitalized with community-acquired pneumonia. Pediatrics. 2017;140(3):e20171013.
19. Wunderink RG, et al. Pneumococcal community-acquired pneumonia detected by serotype-specific urinary antigen detection assays. Clin Infect Dis. 2018;66(10):1504–10.
20. Elberse K, et al. Detection and serotyping of pneumococci in community acquired pneumonia patients without culture using blood and urine samples. BMC Infect Dis. 2015;15:56.
21. Galetto-Lacour A, et al. Elevated inflammatory markers combined with positive pneumococcal urinary antigen are a good predictor of pneumococcal community-acquired pneumonia in children. Pediatr Infect Dis J. 2013;32(11):1175–9.
22. Driscoll AJ, et al. The effect of antibiotic exposure and specimen volume on the detection of bacterial pathogens in children with pneumonia. Clin Infect Dis. 2017;64(suppl_3):S368–77.
23. Miyashita N, et al. Rapid diagnostic method for the identification of mycoplasma pneumoniae respiratory tract infection. J Infect Chemother. 2016;22(5):327–30.
24. Michelow IC, et al. Diagnostic utility and clinical significance of naso- and oropharyngeal samples used in a PCR assay to diagnose mycoplasma pneumoniae infection in children with community-acquired pneumonia. J Clin Microbiol. 2004;42(7):3339–41.
25. Menon PR, et al. A prospective assessment of the role of bronchoscopy and bronchoalveolar lavage in evaluation of children with pulmonary tuberculosis. J Trop Pediatr. 2011;57(5):363–7.
26. Singh M, et al. Role of gastric lavage and bronchoalveolar lavage in the bacteriological diagnosis of childhood pulmonary tuberculosis. Indian Pediatr. 2000;37(9):947–51.
27. Ljungman P, Snydman D, Boeckh M. In: Per L, David S, Michael B, editors. Transplant infections. 4th ed. Cham: Springer; 2016.
28. McNeil MM, et al. Trends in mortality due to invasive mycotic diseases in the United States, 1980-1997. Clin Infect Dis. 2001;33(5):641–7.
29. Lehrnbecher T, Groll AH. Invasive fungal infections in the pediatric population. Expert Rev Anti-Infect Ther. 2011;9(3):275–8.
30. Pana ZD, et al. Epidemiology of invasive fungal disease in children. J Pediatr Infect Dis Soc. 2017;6(suppl_1):S3–S11.
31. Steinbach WJ. Epidemiology of invasive fungal infections in neonates and children. Clin Microbiol Infect. 2010;16(9):1321–7.
32. Crassard N, et al. Invasive aspergillosis and allogeneic hematopoietic stem cell transplantation in children: a 15-year experience. Transpl Infect Dis. 2008;10(3):177–83.
33. Neofytos D, et al. Epidemiology, risk factors and outcomes of invasive aspergillosis in solid organ transplant recipients in the Swiss Transplant Cohort Study. Transpl Infect Dis. 2018;20:e12898.
34. Gerrard JG. Pneumocystis carinii pneumonia in HIV-negative immunocompromised adults. Med J Aust. 1995;162(5):233–5.
35. Gryzan S, et al. Unexpectedly high incidence of Pneumocystis carinii infection after lung-heart transplantation. Implications for lung defense and allograft survival. Am Rev Respir Dis. 1988;137(6):1268–74.
36. Sepkowitz KA. Antibiotic prophylaxis in patients receiving hematopoietic stem cell transplant. Bone Marrow Transplant. 2002;29(5):367–71.
37. Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. Clin Infect Dis. 2002;34(8):1098–107.
38. De Castro N, et al. Occurrence of Pneumocystis jiroveci pneumonia after allogeneic stem cell transplantation: a 6-year retrospective study. Bone Marrow Transplant. 2005;36(10):879–83.
39. Chen CS, et al. Incidence, risk factors, and mortality from pneumonia developing late after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2003;32(5):515–22.
40. Cooley L, et al. Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014. Intern Med J. 2014;44(12b):1350–63.
41. Danion F, et al. Mucormycosis: new developments into a persistently devastating infection. Semin Respir Crit Care Med. 2015;36(5):692–705.
42. Tedder M, et al. Pulmonary mucormycosis: results of medical and surgical therapy. Ann Thorac Surg. 1994;57(4):1044–50.

43. Roden MM, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):634–53.
44. Bitar D, et al. Increasing incidence of zygomycosis (mucormycosis), France, 1997-2006. Emerg Infect Dis. 2009;15(9):1395–401.
45. Park BJ, et al. Invasive non-Aspergillus mold infections in transplant recipients, United States, 2001-2006. Emerg Infect Dis. 2011;17(10):1855–64.
46. Pappas PG, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50(8):1101–11.
47. Kontoyiannis DP, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis. 2010;50(8):1091–100.
48. Dagenais TR, Keller NP. Pathogenesis of Aspergillus fumigatus in invasive aspergillosis. Clin Microbiol Rev. 2009;22(3):447–65.
49. Georgiadou SP, et al. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis. 2011;52(9):1144–55.
50. Saugier-Veber P, et al. Epidemiology and diagnosis of invasive pulmonary aspergillosis in bone marrow transplant patients: results of a 5 year retrospective study. Bone Marrow Transplant. 1993;12(2):121–4.
51. Burgos A, et al. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics. 2008;121(5):e1286–94.
52. von Eiff M, et al. Pulmonary aspergillosis: early diagnosis improves survival. Respiration. 1995;62(6):341–7.
53. Patterson TF, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63(4):e1–e60.
54. Ascioglu S, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis. 2002;34(1):7–14.
55. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. Lancet Infect Dis. 2005;5(10):609–22.
56. Hope WW, et al. Pathogenesis of Aspergillus fumigatus and the kinetics of galactomannan in an in vitro model of early invasive pulmonary aspergillosis: implications for antifungal therapy. J Infect Dis. 2007;195(3):455–66.
57. Sulahian A, et al. Value of antigen detection using an enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric hematology units during a 4-year prospective study. Cancer. 2001;91(2):311–8.
58. Pickering JW, et al. Evaluation of a (1->3)-beta-D-glucan assay for diagnosis of invasive fungal infections. J Clin Microbiol. 2005;43(12):5957–62.
59. Arvanitis M, et al. PCR in diagnosis of invasive aspergillosis: a meta-analysis of diagnostic performance. J Clin Microbiol. 2014;52(10):3731–42.
60. Hoenigl M, et al. Performance of galactomannan, beta-d-glucan, Aspergillus lateral-flow device, conventional culture, and PCR tests with bronchoalveolar lavage fluid for diagnosis of invasive pulmonary aspergillosis. J Clin Microbiol. 2014;52(6):2039–45.
61. Crans CA Jr, Boiselle PM. Imaging features of Pneumocystis carinii pneumonia. Crit Rev Diagn Imaging. 1999;40(4):251–84.
62. Esteves F, et al. Diagnosis of Pneumocystis pneumonia: evaluation of four serologic biomarkers. Clin Microbiol Infect. 2015;21(4):379 e1–10.
63. Pagano L, et al. Pneumocystis carinii pneumonia in patients with malignant haematological diseases: 10 years' experience of infection in GIMEMA centres. Br J Haematol. 2002;117(2):379–86.
64. Azoulay E, et al. Polymerase chain reaction for diagnosing pneumocystis pneumonia in non-HIV immunocompromised patients with pulmonary infiltrates. Chest. 2009;135(3):655–61.
65. Goldman DL, et al. Serologic evidence for *Cryptococcus neoformans* infection in early childhood. Pediatrics. 2001;107(5):E66.
66. Perfect JR, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010;50(3):291–322.
67. Kerkering TM, Duma RJ, Shadomy S. The evolution of pulmonary cryptococcosis: clinical implications from a study of 41 patients with and without compromising host factors. Ann Intern Med. 1981;94(5):611–6.
68. Kohno S, et al. Clinical features of pulmonary cryptococcosis in non-HIV patients in Japan. J Infect Chemother. 2015;21(1):23–30.
69. Singh N, et al. Pulmonary cryptococcosis in solid organ transplant recipients: clinical relevance of serum cryptococcal antigen. Clin Infect Dis. 2008;46(2):e12–8.
70. Danziger-Isakov L, et al. A multicenter consortium to define the epidemiology and outcomes of pediatric solid organ transplant recipients with inpatient respiratory virus infection. J Pediatr Infect Dis Soc. 2018;8:197.
71. Fisher BT, et al. A multicenter consortium to define the epidemiology and outcomes of inpatient respiratory viral infections in pediatric hematopoietic stem cell transplant recipients. J Pediatr Infect Dis Soc. 2017;7:275.
72. Danziger-Isakov L. Infections in children on biologics. Infect Dis Clin N Am. 2018;32(1):225–36.
73. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. Clin Infect Dis. 2010;50(11):1439–47.

74. Danziger-Isakov LA, et al. The risk, prevention, and outcome of cytomegalovirus after pediatric lung transplantation. Transplantation. 2009;87(10):1541–8.
75. Restrepo-Gualteros SM, et al. Characterization of cytomegalovirus lung infection in non-HIV infected children. Viruses. 2014;6(5):2038–51.
76. Burgener EB, et al. Clinical characteristics and outcomes of pediatric patients with CMV DNA detection in bronchoalveolar lavage fluid. Pediatr Pulmonol. 2017;52(1):112–8.
77. Govender K, Jeena P, Parboosing R. Clinical utility of bronchoalveolar lavage cytomegalovirus viral loads in the diagnosis of cytomegalovirus pneumonitis in infants. J Med Virol. 2017;89(6):1080–7.
78. Chemaly RF, et al. Correlation between viral loads of cytomegalovirus in blood and bronchoalveolar lavage specimens from lung transplant recipients determined by histology and immunohistochemistry. J Clin Microbiol. 2004;42(5):2168–72.
79. Westall GP, et al. Human cytomegalovirus load in plasma and bronchoalveolar lavage fluid: a longitudinal study of lung transplant recipients. J Infect Dis. 2004;190(6):1076–83.
80. Marin M, Zhang JX, Seward JF. Near elimination of varicella deaths in the US after implementation of the vaccination program. Pediatrics. 2011;128(2):214–20.
81. Hervas D, et al. How frequent is varicella-associated pneumonia in children? Eur J Clin Microbiol Infect Dis. 2011;30(3):435–7.
82. Mirouse A, et al. Severe varicella-zoster virus pneumonia: a multicenter cohort study. Crit Care. 2017;21(1):137.
83. Brodoefel H, et al. Herpes-Simplex-Virus 1 pneumonia in the immunocompromised host: high-resolution CT patterns in correlation to outcome and follow-up. Eur J Radiol. 2012;81(4):e415–20.
84. Cunha BA, et al. Herpes simplex virus (HSV) pneumonia in a heart transplant: diagnosis and therapy. Heart Lung. 2007;36(1):72–8.
85. Chong S, Kim TS, Cho EY. Herpes simplex virus pneumonia: high-resolution CT findings. Br J Radiol. 2010;83(991):585–9.
86. Kunitomi A, Arima N, Ishikawa T. Epstein-Barr virus-associated post-transplant lymphoproliferative disorders presented as interstitial pneumonia; successful recovery with rituximab. Haematologica. 2007;92(4):e49–52.
87. Siegel MJ, et al. CT of posttransplantation lymphoproliferative disorder in pediatric recipients of lung allograft. AJR Am J Roentgenol. 2003;181(4):1125–31.
88. Marzouk K, et al. Epstein-Barr-virus-induced interstitial lung disease. Curr Opin Pulm Med. 2005;11(5):456–60.
89. Teira P, et al. Primary Epstein-Barr virus infection with pneumonia transmitted by allogeneic bone marrow after transplantation. Clin Infect Dis. 2006;43(7):892–5.
90. Krumbholz A, et al. Epstein-Barr virus-associated pneumonia and bronchiolitis obliterans syndrome in a lung transplant recipient. Med Microbiol Immunol. 2010;199(4):317–22.
91. Liu QF, et al. Epstein-Barr virus-associated pneumonia in patients with post-transplant lymphoproliferative disease after hematopoietic stem cell transplantation. Transpl Infect Dis. 2010;12(4):284–91.
92. Xuan L, et al. Spectrum of Epstein-Barr virus-associated diseases in recipients of allogeneic hematopoietic stem cell transplantation. Transplantation. 2013;96(6):560–6.
93. Swerdlow SH, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90.
94. Costa C, et al. Quantitative detection of Epstein-Barr virus in bronchoalveolar lavage from transplant and nontransplant patients. Transplantation. 2008;86(10):1389–94.
95. Costa C, et al. Quantitative detection of HHV-6 and HHV-7 in transbronchial biopsies from lung transplant recipients. New Microbiol. 2011;34(3):275–80.
96. Carrigan DR, et al. Interstitial pneumonitis associated with human herpesvirus-6 infection after marrow transplantation. Lancet. 1991;338(8760):147–9.
97. Merk J, et al. Fatal pulmonary failure attributable to viral pneumonia with human herpes virus 6 (HHV6) in a young immunocompetent woman. J Intensive Care Med. 2005;20(5):302–6.
98. Buchbinder S, et al. Human herpesvirus 6 is an important pathogen in infectious lung disease after allogeneic bone marrow transplantation. Bone Marrow Transplant. 2000;26(6):639–44.
99. Nakayama T, et al. A case of pneumonitis and encephalitis associated with human herpesvirus 6 (HHV-6) infection after bone marrow transplantation. Br J Radiol. 2010;83(996):e255–8.
100. Sauter A, et al. Spectrum of imaging findings in immunocompromised patients with HHV-6 infection. AJR Am J Roentgenol. 2009;193(5):W373–80.
101. Nwabudike SM, et al. Pulmonary Kaposi Sarcoma: an uncommon cause of respiratory failure in the era of highly active antiretroviral therapy-case report and review of the literature. Case Rep Infect Dis. 2016;2016:9354136.
102. Hayashi M, et al. Kaposi's sarcoma-associated herpesvirus infection in the lung in multicentric Castleman's disease. Intern Med. 1999;38(3):279–82.
103. Muller A, et al. Human herpesvirus type 8 in HIV-infected patients with interstitial pneumonitis. J Infect. 2000;40(3):242–7.
104. Borie R, et al. Pulmonary manifestations of human herpesvirus-8 during HIV infection. Eur Respir J. 2013;42(4):1105–18.
105. Dow DE, Cunningham CK, Buchanan AM. A review of human Herpesvirus 8, the Kaposi's Sarcoma-associated herpesvirus, in the pediatric population. J Pediatr Infect Dis Soc. 2014;3(1):66–76.

106. Sala I, et al. HHV-8-related visceral Kaposi's sarcoma following allogeneic HSCT: report of a pediatric case and literature review. Pediatr Transplant. 2011;15(1):E8–11.
107. Chavez-Bueno S, et al. Intravenous palivizumab and ribavirin combination for respiratory syncytial virus disease in high-risk pediatric patients. Pediatr Infect Dis J. 2007;26(12):1089–93.
108. El Saleeby CM, et al. Risk factors for severe respiratory syncytial virus disease in children with cancer: the importance of lymphopenia and young age. Pediatrics. 2008;121(2):235–43.
109. Rello J, Pop-Vicas A. Clinical review: primary influenza viral pneumonia. Crit Care. 2009;13(6):235.
110. Vilar-Compte D, et al. Influenza in patients with hematological malignancies: experience at two comprehensive cancer centers. J Med Virol. 2018;90(1):50–60.
111. Khanal S, Ghimire P, Dhamoon AS. The repertoire of adenovirus in human disease: the innocuous to the deadly. Biomedicine. 2018;6(1):30.
112. Ariza-Heredia EJ, et al. Clinical and radiological features of respiratory syncytial virus in solid organ transplant recipients: a single-center experience. Transpl Infect Dis. 2012;14(1):64–71.
113. Rolfes MFI, Garg S, Flannery B, Brammer L, Singleton J, Burns E, Jernigan D, Reed C, Olsen S, Bresee J. Estimated influenza illnesses, medical visits, hospitalizations, and deaths averted by vaccination in the United States. 2016.; Available from: https://www.cdc.gov/flu/about/disease/2015-16.htm.
114. Hutspardol S, et al. Significant transplantation-related mortality from respiratory virus infections within the first one hundred days in children after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2015;21(10):1802–7.
115. Kim YJ, et al. Respiratory syncytial virus in hematopoietic cell transplant recipients: factors determining progression to lower respiratory tract disease. J Infect Dis. 2014;209(8):1195–204.
116. Mori M, et al. Risks and prevention of severe RS virus infection among children with immunodeficiency and Down's syndrome. J Infect Chemother. 2014;20(8):455–9.
117. Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. Clin Infect Dis. 1998;27(5):1194–200.
118. Pham TT, Burchette JL Jr, Hale LP. Fatal disseminated adenovirus infections in immunocompromised patients. Am J Clin Pathol. 2003;120(4):575–83.
119. George D, et al. Adenovirus infection in paediatric allogeneic stem cell transplantation recipients is a major independent factor for significantly increasing the risk of treatment related mortality. Br J Haematol. 2012;156(1):99–108.
120. Sanches BF, et al. Multiple parasitic infections in a cardiac transplant recipient. BMJ Case Rep. 2015;2015:bcr2014207033.
121. Abanyie FA, et al. Organ donor screening practices for *Strongyloides stercoralis* infection among US organ procurement organizations. Transpl Infect Dis. 2018;20(3):e12865.
122. Roseman DA, et al. *Strongyloides stercoralis* transmission by kidney transplantation in two recipients from a common donor. Am J Transplant. 2013;13(9):2483–6.
123. Mobley CM, Dhala A, Ghobrial RM. *Strongyloides stercoralis* in solid organ transplantation: early diagnosis gets the worm. Curr Opin Organ Transplant. 2017;22(4):336–44.
124. Paula FM, et al. Molecular diagnosis of *Strongyloides stercoralis* among transplant candidates. Transpl Infect Dis. 2018;20:e12909.

Bronchiectasis and Suppurative Bronchitis

21

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Flexible bronchoscopy (FB), now an essential tool for paediatric, is used for diagnostic and therapeutic purposes in chronic endobronchial suppurative disorders. This chapter discusses the role and findings of flexible bronchoscopy and bronchoalveolar lavage (BAL) in children with bronchiectasis and other airway suppurative lung diseases. Bronchial biopsies are not discussed as its use is currently restricted to research.

Electronic Supplementary Material: The online version of this chapter (https://doi.org/10.1007/978-3-030-54924-4_21) contains supplementary material, which is available to authorized users.

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Brief Overview of Endobronchial Suppuration Disorders in Children

Several conditions are associated with suppurative bronchitis (endobronchial suppuration), all of which share common FB features (macroscopically and BAL findings). Also, since bronchitis is a feature in these diagnostic entities, they share the common feature of wet or productive cough. Thus, in this chapter, we present a broad overview of the more common conditions of suppurative bronchitis seen in paediatric clinical practice. Diffuse panbronchiolitis, another form of airway suppuration with its distinct entity, though infrequently reported in children, is also discussed here. A section on the shared FB features is followed by specific findings related to the diagnostic entities. It is beyond the scope of the chapter to provide an in-depth review of each disease entity, and readers are referred to recent reviews for these.

Bronchiectasis and Chronic Suppurative Lung Disease (CSLD)

Bronchiectasis is the 'end-product' of any condition associated with endobronchial suppura-

S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_21

tion and is associated with a multitude of conditions [1, 2]. Thus, bronchiectasis is a heterogeneous entity whose underlying aetiologies include congenital or genetic conditions, post-infection, aspiration, immunodeficiency, or idiopathic inflammatory conditions [3–7]. Clinically, it is characterized by chronic or recurrent wet cough or sputum production and recurrent pulmonary infections [8, 9]. When severe, other symptoms and signs are found (e.g., haemoptysis, dyspnoea and digital clubbing) [1]. Diagnosis is by a chest high-resolution computed tomography (HRCT). While bronchiectasis is classically described as irreversible abnormal dilatation of the bronchial tree [10], resolution or improvement of the radiological changes is seen for mild cylindrical bronchiectasis when treated [1, 11, 12]. Bronchiectasis is associated with morbidities, and severe disease may progress to respiratory failure and premature death. To date, the pathogenesis of bronchiectasis is still not well defined [13], but the clinical course includes a vicious cycle of infection, airway inflammation and further bronchial wall destruction. The associated impairment of mucociliary clearance promotes the proliferation and colonization of airway pathogens [14]. Consequently, if suboptimally treated or if the disease cannot be controlled, these mechanisms lead to progressive lung damage and accelerated decline of pulmonary function [15]. Intensive treatment aiming at control of symptoms and prevention of exacerbations can delay disease progression and improve quality of life [1].

While the global prevalence of bronchiectasis being undetermined, the prevalence and incidence of bronchiectasis are on the rise worldwide, particularly among the underprivileged populations. The increasing awareness of clinicians and accessibility of CT scan has increased the ability to confirm the diagnosis [7].

Chronic suppurative lung disease (CSLD) is a broad descriptive term that has been specifically applied to children who have the clinical features of bronchiectasis but lack radiological changes that is needed for the diagnosis [16, 17]. That is, CSLD may be the prodrome of bronchiectasis with the same features of early cylindrical bronchiectasis except for the CT findings [1]. Bronchiectasis, CSLD and protracted bacterial bronchitis (PBB) are speculated to be a spectrum of lung diseases that share the common feature of endobronchial suppuration.

Protracted Bacterial Bronchitis (PBB)

PBB, the commonest cause of chronic wet cough in some settings [18, 19], was first described in 2006 [20]. It is deemed a pre-CSLD condition [1, 17]. PBB, a relatively new diagnostic entity, is characterized by persistent endobronchial bacterial infection. It is clinically defined as chronic wet cough of more than 4 weeks in the absence of symptoms and signs of other aetiologies for the wet cough [21]. Confirmation occurs if resolved following a 2-week course of appropriate antibiotic treatment (usually amoxicillin–clavulanate). While more common in young children, PBB causes chronic wet/productive cough in all ages [18, 19]. Recurrent or persistent PBB can cause chronic airway inflammation that damages the epithelium and impairs removal of airway secretions and eventually manifests as CSLD or bronchiectasis [22]. Readers are referred to recent Australian, US [21, 23, 24], and European Respiratory Society taskforce reviews [19].

Primary Ciliary Dyskinesia (PCD)

PCD, a heterogeneous autosomal recessive disorder associated with structural or functional abnormalities of the airway cilia, causes chronic oto-sino-pulmonary diseases [25]. Children with PCD manifest unexplained transient neonatal respiratory distress and chronic wet cough from infancy. Chronic rhinosinusitis, chronic otitis media with effusion and infertility from immotile sperm are also part of the typical clinical presentation [26, 27]. About half have situs inversus totalis. A small subset will have heterotoxy with complex congenital heart disease. Other ciliopathies, including retinitis pigmentosa (X-linked inheritance), polycystic kidney disease, liver disease and hydrocephalus, have all been rarely described occasionally in association with PCD

[27, 28]. The triad of chronic rhinosinusitis, situs inversus totalis and bronchiectasis is known as Kartagener syndrome. The estimated incidence of PCD is 1 in 10,000–20,000 live births [26]. This is probably underestimated as the diagnosis of PCD is often missed or delayed. The median age of diagnosis is reported as 5.3 years of age in Europe [29].

The diagnosis of PCD is challenging due to its heterogeneity, the wide range of disease severity, non-specific clinical features (overlap with viral respiratory tract infections in young children), and unavailability of a single gold standard test that encompasses the entire spectrum of PCD. A recent systematic meta-analysis review of 52 studies on PCD revealed a wide spectrum of symptoms prevalence which highlighted the difficulty in describing the full clinical picture of PCD based on the published data [30]. The diagnosis requires a combination of clinical history and technically demanding tests such as nasal nitric oxide levels, high-speed video microscopy analysis, transmission electron microscopy and genetic mutation study. To date, there are about 30 mutations that have been reported to be associated with PCD, and the number of genes involved is still growing [26]. Readers are referred to recent guidelines on diagnosing PCD [31, 32]. Ciliary dysfunction in PCD impedes mucociliary clearance, which gives rise to stagnation of the airway secretions and thus leads to recurrent endobronchial infections and eventually the development of bronchiectasis though generally at a much slower rate that is seen with cystic fibrosis.

Cystic Fibrosis (CF)

CF is currently the commonest inherited suppurative lung disease affecting Caucasian populations [33]. It is an autosomal recessive disease caused by defect of the cystic fibrosis transmembrane conductance regulator (CFTR) gene at the long arm of Chromosome 7 with >2000 gene mutations, but not all of the mutations are deleterious, identified and various structural or functional defects in the CFTR protein [34]. CF affects multiple organs, primarily the airways, and is also associated with other conditions such as chronic sinusitis, pancreatic insufficiency, hepatobiliary disease, diabetes, osteoporosis and absence of vas deferens. Mutation of CFTR gene results in failed transport of chloride through the CFTR and ion channels, which leads to dehydration of the airway epithelium and thickened endobronchial secretions. Consequently, mucociliary clearance is impaired, thus predisposing to pathogen colonization and repeated endobronchial infections. These mechanisms result in the development of bronchiectasis and subsequent respiratory failure. With the advent of newborn screening programs and aggressive treatment at centres of care for cystic fibrosis, the outcome of this potential debilitating and life-limiting disease has markedly improved in the recent decades. Even prior to the availability of new CFTR-targeted therapies, people with CF attained median age of survivals of 50 years in some developed countries [34].

Diffuse Panbronchiolitis (DPB)

DPB is an idiopathic inflammatory disease characterized by chronic sinobronchial infection. It typically affects the respiratory bronchioles, leading to a progressive suppurative and severe obstructive and restrictive lung disease [35, 36]. DPB was first described in 1960s by a group of Japanese, and the reported prevalence in Japan in 1980s was 11 cases per 100,000 people [37, 38]. Multiple reports have also come from China and South Korea. In addition to the many cases of Southeast Asians, 22 case reports included Caucasians from North and South America, Europe, Australia and Turkey. Case reports also included one instance of African descent, one Samoan and one Australian Aborigine. But its prevalence worldwide is not known. Chronic airway inflammation in DPB is frequently preceded by chronic sinusitis, often present for many years prior to respiratory symptoms. Similar to other endobronchial disorders, damage to epithelial cells leads to the development of extensive bronchiectasis [38]. DPB usually occurs in the second to fifth decade of life. However, some of the reported cases describe symptoms beginning in

childhood, and there are case reports involving adolescents and children [39–42]. The common clinical feature is chronic wet cough with copious sputum, followed by exertional dyspnoea. Chest examination reveals crackles, wheeze, or both. HRCT typically shows nodular shadows distributed in a centrilobular fashion and, in advance diseases, features of bronchiectasis [38]. Patients with DPB before the era of macrolides had a poor prognosis, with 5- and 10-year survival rates of 62.1 and 33.2%, respectively [38]. The use of long-term macrolide antibiotics as anti-inflammatory and immunoregulatory agent has markedly improved the outcome, by increasing the 10-year survival rate to >90% [43].

Flexible Bronchoscopy Findings in Endobronchial Suppurative Disorders

There are common and specific features across the different diagnostic entities discussed above. In this section, we describe the general, both macroscopic and microscopic, followed by more specific findings in each form of the above diseases.

Common Generic Bronchoscopic Findings in Endobronchial Suppuration

Bronchoscopic findings encountered in endobronchial suppurative disorders can be divided into macroscopic (i.e., findings visualized during FB) and microscopic (findings from BAL fluid). Across the conditions, there is active research on airway inflammation to assess the severity of the disease and monitor disease progression or response to therapies, but we focus on clinical issues.

Macroscopic Findings of Bronchitis

Macroscopic FB findings consist of visualized data of the airways secretions (amount and colour), mucosal appearance and structure of the tracheobronchial tree.

Airway Secretions, Mucosal Appearance and Bronchitis Scores

Bronchitis (inflammation of the airways) and increased airway secretion are part of the active endobronchial suppuration process. In clinical practice, the term bronchitis has been used to describe what a bronchoscopist perceives as airway inflammation during the procedure although there is no standardized or validated definition to date.

In all the suppurative bronchitis conditions, copious amount of purulent secretion may be present and obscure the airway lumens and/or impact the bronchi causing lobar or segmental atelectasis (Figs. 21.1 and 21.2). In adults, airway secretions can be easily collected as sputum, and the simple observation on the sputum colour correlates with airway inflammation and clinical findings. The sputum colour (nine-point colour chart) to quantify airway inflammation objectively [44] is based on the concept that the green heme-containing protein, MPO, is contained within azurophil granules of neutrophils and pro-inflammatory monocytes, giving these cells a distinctive deep green colour. The UK group showed that sputum colour correlated strongly with the underlying bronchial inflammatory mediators, such as myeloperoxidase, interleukin 8, leucocyte elastase and secretory leucocyte proteinase inhibitor [44]. Similarly, Murray et al. demonstrated increased sputum purulence (three major grades of colour) related with increased neutrophilic airway inflammation in adults with non-CF bronchiectasis [45].

As most young children do not expectorate, the quantification and evaluation of sputum production is not feasible. A FB airway secretion scoring system (BS) evaluating the amount of secretions and the number of bronchi involved (grading ranged from 1 to 6) has been developed and validated [46]. BS grades significantly correlated with the airway cellularity ($r = 0.36$, $p < 0.0001$), neutrophilia ($r = 0.41$, $p < 0.0001$), and infective state ($p = 0.016$) [46]. However, this scoring system only focused on the secretions in the airway lumen and did not consider the colour of the secretions or the airway wall appearance.

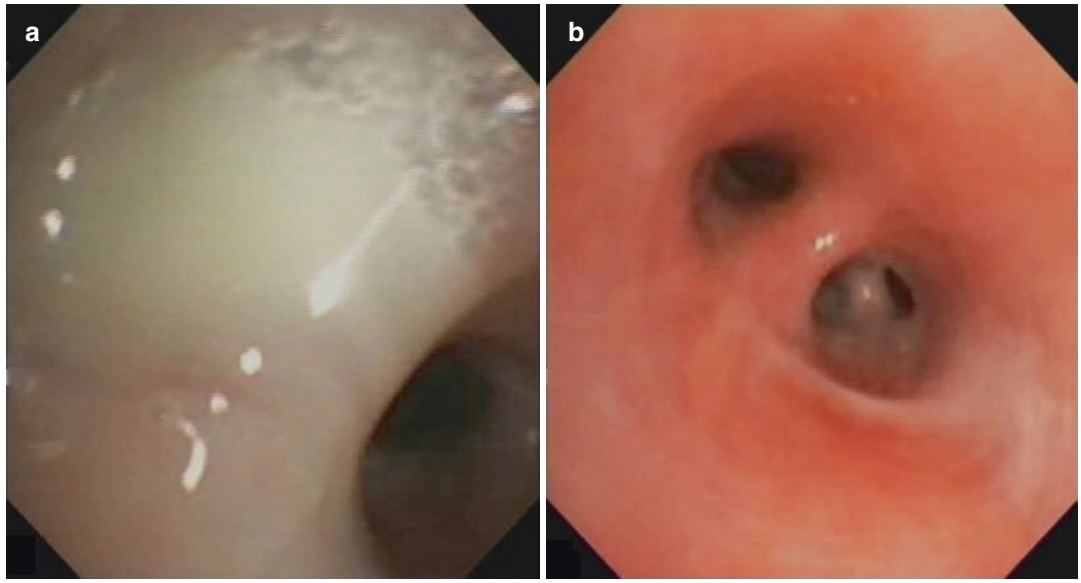

Fig. 21.1 A child with non-CF bronchiectasis. (**a**) Copious purulent secretions obscuring the lumens of right middle lobe bronchi. (**b**) RML post suctioning of purulent secretions. Please see video for the bronchoscopy

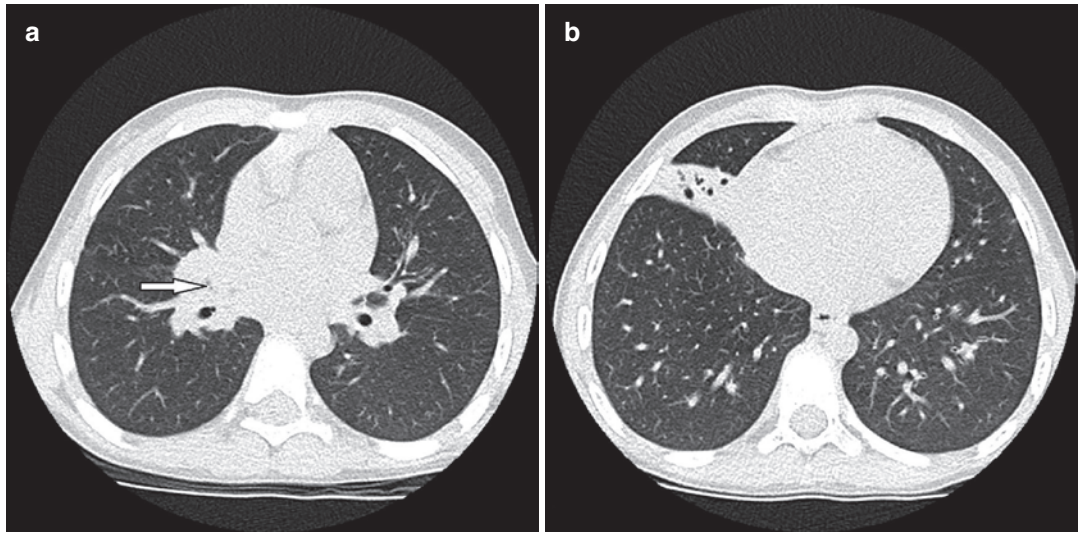

Fig. 21.2 (**a**) Obstructed RML opening on CT scan of chest (arrow) of the patient described in Fig. 21.1. (**b**) RML atelectasis resulted from the proximal obstruction

In adults, a semiquantitative bronchoscopic scoring system (bronchitis index, BI) described intraluminal airway inflammation in three groups of subjects (cigarette smokers with chronic bronchitis, smokers without bronchitis and non-smoker healthy volunteers). The index based on mucosal fragility, oedema, erythema and secretions was developed [47]. The BI was found to be elevated in the group with chronic bronchitis (13.2 ± 0.5) compared with both asymptomatic smokers (8.5 ± 0.9, $p < 0.0005$) and normal volunteers (2.3 ± 0.6, $p < 0.0001$). The BI also posi-

tively correlated with the bronchial neutrophil percentage ($r = 0.28$, $p = 0.015$) [48].

To date, there is no published validated endoscopic scoring system for bronchitis in children which includes both the airway secretion and mucosal characteristics. Descriptions of FB airway inflammation include the presence of mucosal oedema, hyperaemia, hypertrophic submucosal glands (cobblestone pattern), and/or longitudinal mucosal folds [49] and non-descriptive 'bronchitis' [50]. Comparing with endobronchial biopsy depicting airway inflammation in 13 children, Smith et al. mentioned endoscopic appearance of 'bronchitis' [50]. De Baets et al. reported that 64% of the 124 children with recurrent cough and wheeze had FB macroscopic airway mucosal inflammation [49], defined as mucosal oedema, hyperaemia, hypertrophic submucosal glands and/or longitudinal mucosal folds. However, none of these studies [49, 50] provided any reference images nor quantified the severity.

Recently, we developed a bronchitis scoring system looking at the amount and colour of secretions and the mucosal appearance that involves mucosal oedema, erythema, pallor and ridging (mucosal folds, Fig. 21.3) [51, 52]. We initially reviewed bronchoscopy recordings of 100 children who underwent flexible bronchoscopy in a tertiary referral centre retrospectively [51]. An experimental bronchitis scoring system ($BScore_{exp}$) was developed, based on the amount of airway secretions [46], the colour of secretions (using the BronkoTest sputum colour chart), and macroscopic appearance of the lower airways (scored according to the severity of oedema, ridging, erythema and pallor). This was based on a prior definition accompanied with pictorial chart for reference. We found good to excellent inter-rater agreements for secretion amount and colour (weighted kappa value, $k = 0.87$ and 0.86 respectively), and moderate or good for the mucosal appearance components ($k = 0.48$ for oedema, 0.40 for erythema, 0.54 for ridging and 0.64 for pallor) [51].

We are currently using $BScore_{exp}$ to validate the scoring system in a prospective cohort involving 142 children (16 with CF), which also showed positive correlation between the secretion amount ($r = 0.42$, $p = 0.0001$), colour ($r = 0.46$, $p = 0.0001$), mucosal oedema ($r = 0.42$, $p = 0.0001$), erythema ($r = 0.30$, $p = 0.0001$), ridging ($r = 0.11$, $p = 0.177$), and the BAL neutrophil percentage (unpublished data). Our pre-

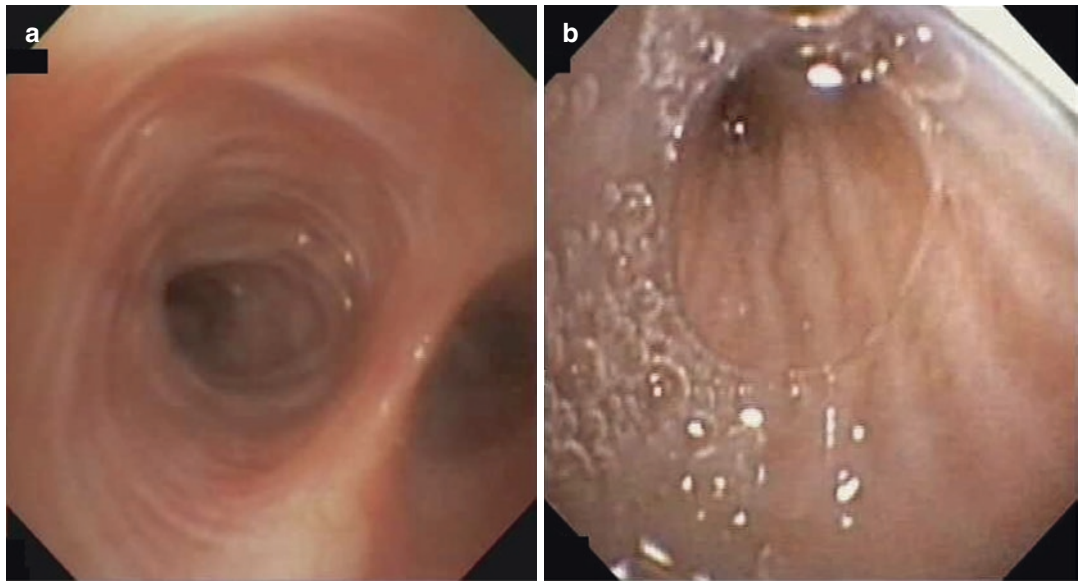

Fig. 21.3 Bronchoscopic appearance of ridging (mucosal folds). (**a**) Circumferential ridging. (**b**) Longitudinal ridging with mucoid secretions

liminary analyses found that a high area (0.84, 95% CI 0.76–0.90) under the receiver operating characteristic curve (aROC) compared with BAL neutrophils of >10% can be obtained using the BScore by the summation scores of all components except pallor. This FB-based tool to assess suppurative bronchitis may have clinical and research utility. The data show that the FB macroscopic findings of airway suppuration in children can be standardized and semi-quantified.

Tracheobronchial Abnormalities – Airway Malacia

Malacic airways are commonly encountered during FB in children with suppurative lung disease. FB is invariably the most useful tool that allows direct inspection of the airway dynamics, thus offering confirmative diagnosis of malacia, that is, softening of the airway cartilage seen as airway collapse maximally at the end of expiration [53]. Diagnosis of malacic airways can be challenging as there is wide range of bronchoscopic appearances, and to date, there is no validated standardized objective measurement of these lesions [53]. Kompare and Weinberger reported a high percentage of (74%) tracheomalacia (TM) (Fig. 21.4) and/or bronchomalacia (Fig. 21.5) in young children <60 months with PBB [54]. Wurzel et al. found a similar rate (68%) in their PBB cohort, but this was also not significantly different from the controls (53% in children with chronic respiratory symptoms but no PBB) [55]. Goyal et al. reported 41% for tracheomalacia or tracheobronchomalacia in their case series of CSLD (absence of bronchiectasis in chest CT scan) [56]. When comparing three groups of suppurative lung diseases (PBB, bronchiectasis and CF), de Vries et al. identified significant differences in the prevalence of malacia; while PBB group had the highest rate of 71% and bronchiectasis had 47%, the diagnosis of malacia was only found in 9% of children with CF in one report [9] and 15% (15/97) in another report [57]. The latter publication also found that *Pseudomonas aeruginosa* infection occurred 1.3 years earlier among children with TM ($P < 0.01$). All these values far exceed the estimated incidence of primary airway malacia of 1 in 2100 live births [58].

Whether chronic suppuration is the primary event that causes tracheal or bronchial abnormality (malacia) or the malacia is the primary factor that results in PBB remains debat-

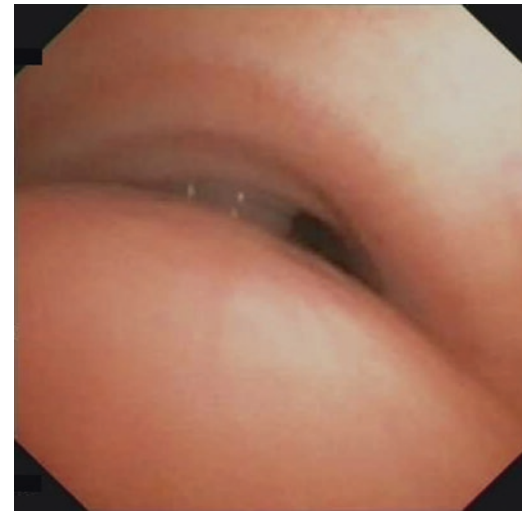

Fig. 21.4 Bronchoscopic appearance of tracheomalacia in a child who previously had a tracheoesophageal fistula repair. Airway suppuration was present during FB. The BAL showed classical findings of children with airway suppuration with airway neutrophilia (62.6%) and infection with common respiratory pathogens (here *Haemophilus influenzae* at 10^5 cfu/ml BAL)

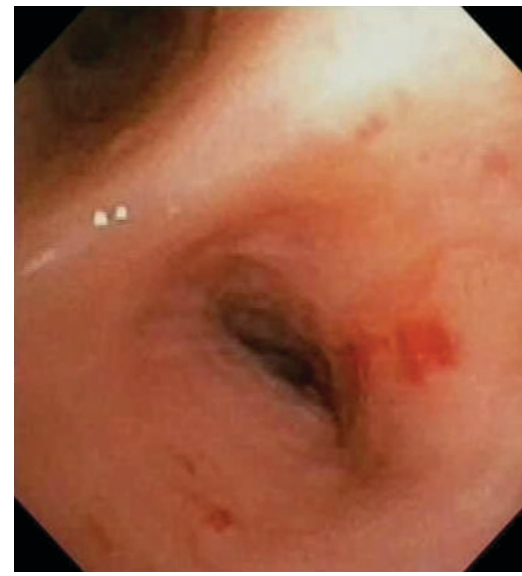

Fig. 21.5 Malacia of the lingula of the left upper lobe in a child with non- CF bronchiectasis

able. Though malacia may impede the airway mucus clearance and its clinical profiles are generally worse than similar respiratory illnesses in children without airway malacia, de Vries et al. found no significant difference in BAL infection rates or microbiology between children with or without malacia [9]. Visualizing malacia requires sufficiently light sedation that spontaneous breathing and perhaps even occasional coughing can occur. General anaesthesia may prevent seeing malacia other than severe tracheomalacia as in Fig. 21.4.

BAL Findings

Airway Cellularity and Inflammatory Biomarkers

Endobronchial suppuration is generally associated with airway neutrophilic inflammation, although there is a wide range neutrophilia ranging from 6.5% to 89% [9, 55, 59, 60]. A study of the BAL cellularity data across three forms of endobronchial suppuration (PBB, bronchiectasis and CF) revealed that the median neutrophil percentage was significantly higher in children with CF (68%) compared to children with PBB (36%) and bronchiectasis (22%) [9]. To date, there is no comparison on BAL cellularity between these groups and PCD, but a sputum-based study described that children with both CF and PCD had high neutrophil percentage (median 96%) during pulmonary exacerbations [61].

Airway inflammatory biomarkers including neutrophil elastase, interleukin (IL)-8, active matrix metalloproteinase 9 (MMP-9), and transforming growth factor-β_1 (TGF β_1) are elevated in endobronchial bacterial infections [62–64]. The IL-8 acts as a neutrophil activator and chemoattractant, which stimulates secretion of MMP-9 from intracytoplasmic neutrophil granules, whereas MMP-9 that is synthesized and stored in the neutrophils potentiates the IL-8 activity by altering the cytokine's amino terminal processing. Given these interactions and the strong correlation, it is postulated that there is a positive feedback loop between these two biomarkers and recruited airway neutrophils. This results in a cycle of chronic inflammatory process during endobronchial suppuration [62]. However, at present, there is no known inflammatory marker predictive of the clinical course of the diseases.

Airway Microbiology

Chronic suppuration usually reflects airway infection, and knowledge of the airway bacteriology allows targeted and effective antimicrobial therapy. How to undertake BAL is the focus of another chapter. Specific to suppurative airway disease, the microbiological yield is higher when multiple lobes are lavaged [65, 66]. As the severity of airway disease may vary between lobes, bacteria distribution may be heterogeneously spread [67]. It is beyond the scope of this chapter to present data comparing sputum to BAL microbiology, but it is generally accepted that BAL is the gold standard (with less upper airway contamination) [68–70] and generally provides a higher yield compared to sputum [71, 72].

Quantitative bacteriology (expressed as colony forming unit (cfu) single bacterial growth per ml of BAL) is used to define airway infection [68] as BAL culture can be contaminated by upper airway pathogens. Studies that do not undertake or report quantitative bacteriology should be interpreted with caution. In published data involving children with airway suppuration, the threshold density used to define lower airway infection vary among studies and range from 10^2 to 10^5 cfu/ml BAL [68]. The recommended threshold density was established for children with CF at $\geq 10^5$ cfu/ml [70]. For other suppurative disorders, $\geq 10^4$ cfu/ml is used [68].

Young children with PBB, CSLD/bronchiectasis and PCD have a fairly similar microbiological profile. The commonest bacteria isolated from the lower airways of those disorders are *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis* [9, 11, 56, 59, 60, 62, 71]. Haemophilus, Streptococcus and Moraxella are also frequently cultured in young infants and preschool children with CF. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are associated with increased morbidity and mortality in chronic infection of CF. They are also frequently detected in older children and adults with non-CF bronchiectasis or PCD [71].

Pseudomonas aeruginosa can also be found in diffuse panbronchiolitis. The BAL microbiology would be dependent on many factors, for example, the clinical state (stable vs exacerbation) [73], vaccinations received [74, 75], medications received (e.g., azithromycin) [68] and underlying disease (CF vs PBB) [76], and age (Pseudomonas more likely in older child with CF).

Besides bacteria, fungi and protozoa, viruses are commonly found in isolation or coexisting with a bacterial infection in suppurative bronchitis [9]. Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) by polymerase chain reaction (PCR) have also been described in children with PBB (26% and 17%, respectively) and bronchiectasis (27% and 29%, respectively) [9]. However, the clinical significance of these is unknown, as these organisms are not generally specifically treated other than for allergic bronchopulmonary aspergillosis.

Biofilm

Biofilms are defined as surface-associated microbial communities, surrounded by an extracellular polymeric substance (EPS) matrix [77]. Biofilms are typically detected in chronic diseases that are recalcitrant to host immune responses and antimicrobial actions. They are proposed to function as a nutrient source in nutrient-depleted environments. This can result in a stationary phase-like dormancy within the biofilm, which may be responsible for the reduced antibiotic susceptibility.

Airway biofilms have been demonstrated in the BAL of children with airway suppuration [78–80], specifically in children with CF [78, 79] and bronchiectasis [80]. The latter study [80] involving children with bronchiectasis (who do not have CF or *Pseudomonas aeruginosa*) reported that multiple (three to seven) different organisms including *H. influenzae, S. pneumoniae* and *M. catarrhalis* were isolated from the BAL of children where biofilm was identified. The study [80] also described that biofilm was more commonly found in the second lavage, which is routinely used for cytology and inflammation studies [81] (c.f. the first lavage, which is used for microbiology evaluation).

Disease-Specific Bronchoscopy Findings

In addition to the findings described above that are common to the suppurative conditions, the following summarizes published data that are specific to the diagnostic entities.

Bronchiectasis and CSLD

One study of bronchiectasis where FB was routinely performed identified lower airway eosinophilia, antibiotic-resistant respiratory pathogens and an unexpected inhaled foreign body. A change in management was observed in 41% of 56 children studied as a result of those findings [60].

Macroscopic Findings

An Australian study of 33 Indigenous children with CSLD (28 had radiological bronchiectasis) who underwent bronchoscopy yielded five different airway macroscopic findings [82]: I (mucosal abnormality/inflammation only, 58.3%), II (bronchomalacia, 18.8%), III (obliterative-like, 16.7%), IV (malacia/obliterative-like combination, 4.2%), and

V (no abnormality, 2.1%). A bronchus was considered to be obliterative-like when the airway opening was absent or markedly reduced when compared to the adjacent segmental opening (Fig. 21.6). This lesion was found in 10 out of 33 children (two had concomitant malacia) in their segmental or subsegmental bronchi. This corresponded to the site of abnormality seen on the chest HRCT scan [82]. In 93 children, a Greek study described that a scoring system reflecting severity of bronchiectasis on HRCT correlated with the type III (OR 5.44, 95% CI 1.92–15.40, $p = 0.001$) and type IV (OR 8.91, 95% CI 2.53–15.42, $p = 0.001$) bronchoscopic airway lesions as well as with BAL % neutrophils ($r = 0.23$, $p = 0.036$) [83].

Other possible associated conditions that related to the underlying aetiologies may be detected during FB in children with bronchiectasis/CSLD [60, 84, 85]. For instance, a missed foreign body or granulomatous lesion may be seen obstructing the distal airway causing localized

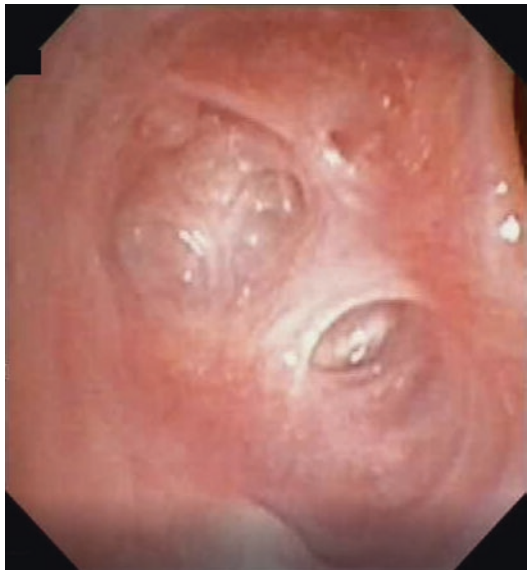

Fig. 21.6 Obliterative-like lesion in bronchiectasis – in RB4a

bronchiectasis [86]. Middle lobe syndrome presents with recurrent atelectasis, or pneumonia is reported in 1% of children with bronchiectasis [11]. Furthermore, other rarer congenital structural abnormalities of the tracheobronchial tree such as tracheal stenosis with or without complete ring, tracheal bronchus, H-type tracheo-esophageal fistula, Mounier-Kuhn syndrome (tracheobronchomegaly), and Williams–Campbell syndrome (defective subsegmental bronchial wall cartilage) may also be diagnosed during FB.

BAL Findings

Generally, neutrophilic airway inflammation is found in children with bronchiectasis/CSLD particularly prior to treatment [59]. However, airway neutrophilia may be absent in the stable state (post-treatment) or when the children are receiving azithromycin [68]. However, an Australian study reported that a significant percentage (34%) of indigenous children with newly diagnosed bronchiectasis have additional airway eosinophilia (>2.5%) from BAL fluid, which may be related to parasitic infections [60].

Protracted Bacterial Bronchitis

While the original microbiologic-based case definition of PBB requires a confirmatory positive bacterial growth from the lower airway specimen, either sputum or BAL fluid [21], most centres reserve FB-BAL to those who do not respond to empirical treatment with appropriate antibiotics or clinical relapse [87]. However, recurrences were observed to occur in over half of young children with PBB, and confirmation with a BAL and determination of airway malacia may be useful [54].

Macroscopic Findings

Purulent airway secretions are common bronchoscopic findings in children with PBB [17, 19]. Emiralioglu et al. [88] reported purulent bronchitis in approximately 50% of children with suspected PBB (n = 31). Conversely, bronchoscopy findings can be normal when the respiratory symptoms resolved. Airway malacia is another common association in PBB [9, 54, 55, 88], raising the possibility of a causal relationship (in either direction) between these two conditions. Though bacterial infection might in some cases be a primary event that causes tracheal or bronchial damage leading to malacia, it is more likely that the malacia is the primary risk factor that results in PBB. This is supported by the observation of spontaneous remission of malacia with treatment and time that generally occurs as the airways grow larger and mucociliary clearance improves [54]. Apart from the aforementioned, there should be no other positive bronchoscopic findings that explain the clinical symptoms in PBB (diagnosis of exclusion).

BAL Findings

An Australian study reported that children with PBB had significantly higher white cell count (WCC), neutrophil percentage (% neutrophils), absolute neutrophil values, IL-8 and active MMP-9 levels, and lower macrophage percentage when compared to children with cough due to other causes or controls with no cough [62]. The IL-8 and active MMP-9 levels correlated

with the % neutrophils ($r = 0.66$ and $r = 0.48$ respectively, $p < 0.001$). The same study also found that innate immunity signalling receptors and the toll-like receptors (TLRs), both TLR-2 and TLR-4, had significantly higher expression levels in the PBB group (who all had positive aerobic culture results). This profile supports that the speculation of airway neutrophilia in PBB is mediated by innate immune activation [62].

High rates of viral–bacterial coinfection and markedly elevated airway neutrophil percentage were apparent in PBB. Wurzel et al. found that human adenovirus (HAdV) was significantly more likely to be detected in the lower airways of children with PBB (23%) compared with control subjects and was associated with higher levels of blood NK cells and airway neutrophilia, indicating a systemic and airway immune response to the virus [55]. A similar percentage of HAdV was also noticed in non-CF bronchiectasis but not in CF children (in another cohort) [9]. However, how this viral infection contributes to the pathogenesis of the diseases is yet to be determined.

Primary Ciliary Dyskinesia

Given the presumed rarity of the disease, partly due to the complexity in making the diagnosis, published data on bronchoscopy findings in children with PCD are scarce. Further, FB is not routinely performed in children diagnosed as PCD unless clinically indicated [28].

Macroscopic Findings

As the prevalence of chronic rhinosinusitis (over 50%) and nasal polyps (up to 18%) is higher in PCD than in the general population (0.1% in children) [28, 32, 89], these findings may be seen when examining the upper airway of these children. Situs inversus totalis is observed in about 50% of PCD [32]. Varying degrees of partial heterotaxy or isomerism are seen less frequently. In a case report of three young children with PCD, bronchitis was visualized in all three: two had situs inversus totalis and one did not [90].

BAL Findings

The lower airway cellularity and microbiology of PCD are understudied. To date, there are no published data from the BAL in children with PCD alone. A consortium involving multiple US/Canadian sites examined the sputum of 416 definite or probable PCD (median age 11 years, range 0.5–75) and reported that overall microbial prevalence was higher in PCD vs non-PCD and CF for *H. influenzae* (32% vs 25% and 26%). Prevalence was lower for PCD and non-PCD vs CF for *P. aeruginosa* (32% and 20% vs 59%). Prevalence of *P. aeruginosa* was increased among adolescent PCD patients when compared to non-PCD (39% vs 12%) but less than that found in CF group (60%) [91]. Organisms isolated from the three reported children with PCD were *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus* [90].

Cystic Fibrosis

Cystic fibrosis is the most widely studied endobronchial suppurative disease. Most CF patients, 89% in a CF centre in the United States (US) [57], would have at least one bronchoscopy done for diagnostic (BAL culture) or therapeutic (impacted mucus) purposes.

Macroscopic Findings

Children with CF may have different degrees of bronchitis depending on the stage and severity of the disease. Secretions in CF tend to be viscous. In progressive or advance disease, mucus impaction leading to a lobar or segmental atelectasis is not uncommon. A therapeutic lavage is often indicated to clear the impacted mucus plugs (Fig. 21.7). Bronchoscopic instillation of recombinant human deoxyribonuclease (rhDnase) is also reported to be useful and resulted radiological and clinical improvement of the atelectasis [92].

The presence of rubbery or caulk-like mucus plug in the airway lumen, what used to be described as plastic bronchitis, should raise the suspicion of allergic bronchopulmonary aspergillosis (ABPA). ABPA was classically described in older children and adults with CF or asthma. The

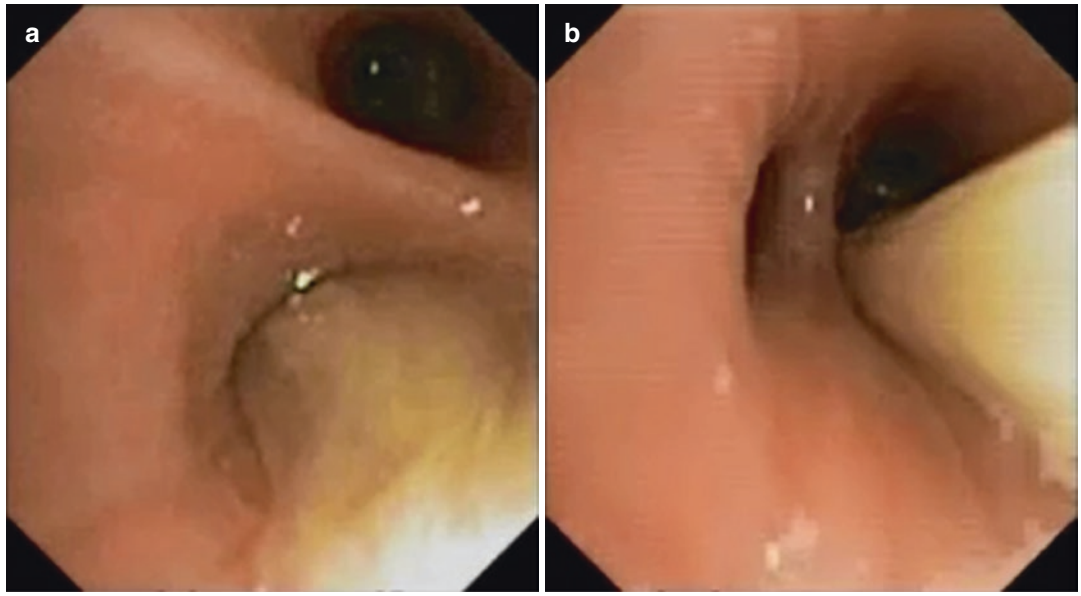

Fig. 21.7 Mucus plug in the posterior basal segment (RB10) of the right lower lobe in a child with cystic fibrosis. (**a**) Plug in RB10. (**b**) Removal of the plug. Please see video for the bronchoscopy

reported prevalence in CF varies, influenced by regional differences and different diagnostic criteria [93]. Data from the Epidemiologic Registry of Cystic Fibrosis (ERCF) gathered from 224 European CF centres revealed an overall prevalence of 7.8% (range 2.1–13.6%) [94], whereas a few centres reported higher rates up to 22% [95]. FB has a specific diagnostic (to obtain BAL) and therapeutic (to remove impacted plastic bronchitis) role in children with aspergillus lung disease (Figs. 21.8, 21.9, and 21.10).

Obliterative lesions described in children with CSLD/bronchiectasis [82] were subsequently also reported in three adult CF patients (one post-lung transplantation) [96], but have not been yet described in children with CF. Whether the pathogenesis of these obliterative lesions in adults is identical to the those in non-CF children is unclear.

Though less frequent when compared with PBB and non-CF bronchiectasis, tracheomalacia was documented in 15% (15 out of 97) of children with CF in a US cohort [57] and 9% ($n = 53$) in Australia [9]. These children with tracheomalacia were associated with decreased initial FEV1 values and significantly earlier acquisition of *P. aeruginosa* [57]. Further, CF patients with tracheomalacia generally had more severe CFTR

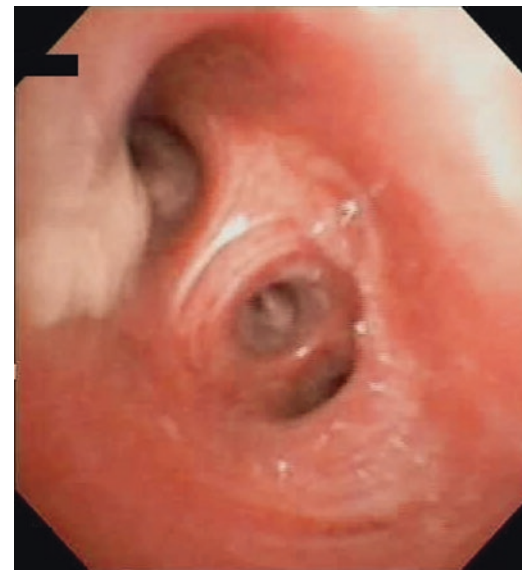

Fig. 21.8 Mucus plug in the left upper lobe of a CF child with APBA. The corresponding CXRs pre and post bronchoscopy are depicted in Fig. 21.9

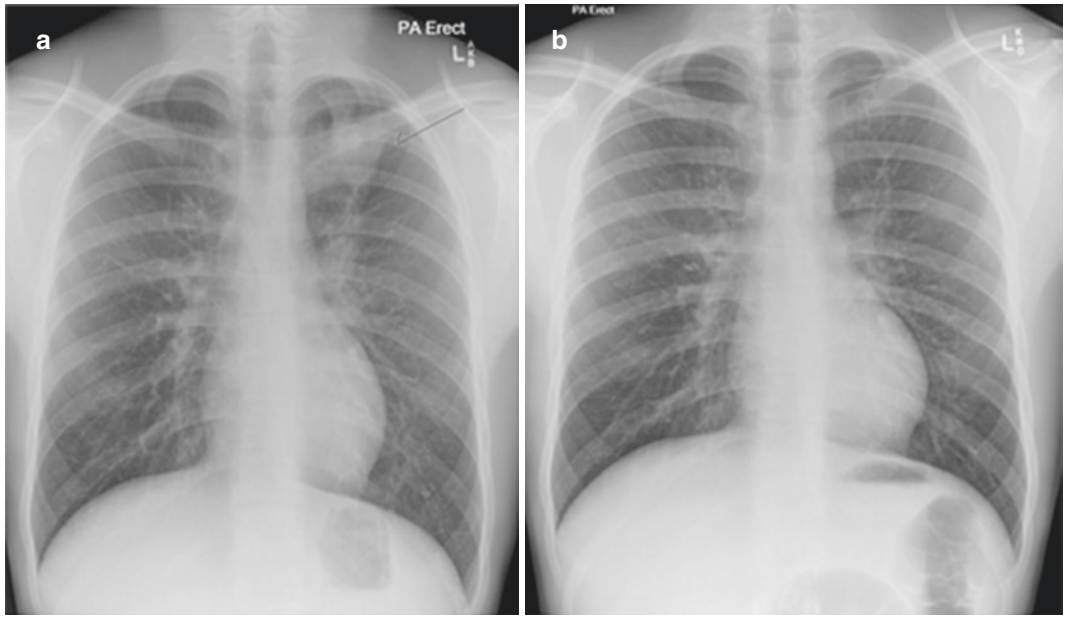

Fig. 21.9 Chest radiograph of the same patient in Fig. 21.8 showed left upper lobe segmental atelectasis (arrow), before (**a**) and after (**b**) a therapeutic bronchoscopy

mutations, but there was no differences in BAL fluid % neutrophils or median age of diagnosis of bronchiectasis when compared to CF patients without tracheomalacia. These findings led to the hypothesis that some tracheomalacia might develop as a consequence of repeated airway infections, and some might be present congenitally and subsequently worsening due to chronic inflammation [57].

BAL Findings

In children with a pulmonary exacerbation of CF, a pattern of inflammation in the airway lumen (elevated concentration in all inflammatory cell types) and bronchial mucosa (higher numbers of lymphocytes and macrophages, but not of neutrophils) has been described [97]. Whether this compartmentalized inflammatory response is distinctive to CF is unknown.

The BAL microbiological profiles are diverse in children with CF. *Staphylococcus aureus, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Burkholderia cepacia, Candida albicans, Aspergillus fumigatus* and *Escherichia coli* are among the pathogens isolated from the lower airway of children with CF [98, 99]. The diversity of the microbiological profile decreases when the CF pulmonary disease advances, with frequent isolation of non-tuberculous Mycobacteria (particularly *Mycobacterium avium complex* and *M. abscessus*) complicating the management of these patients [100].

Diffuse Panbronchiolitis

Very limited data are available in children or adults for bronchoscopic in comparison with other endobronchial diseases. The diagnostic hallmarks of DPB are the presence of multiple centrilobular nodules with tree-in-bud appearance seen on high-resolution CT scan. On biopsy, the inflammatory changes seen in peribronchial tissues consist of thickening of the respiratory bronchiolar wall, thickening of peribronchiolar tissues and bronchial infiltration by lymphocyte plasma cells and inflammatory cytokines such as IL-1β and IL-8 [40]. A marked clinical improvement to macrolide monotherapy can provide a clinical diagnosis that may avoid invasive diagnostic tools including bronchoscopy.

To date, there are only few published case reports of childhood DPB in the English literature, with the youngest of 10 years old

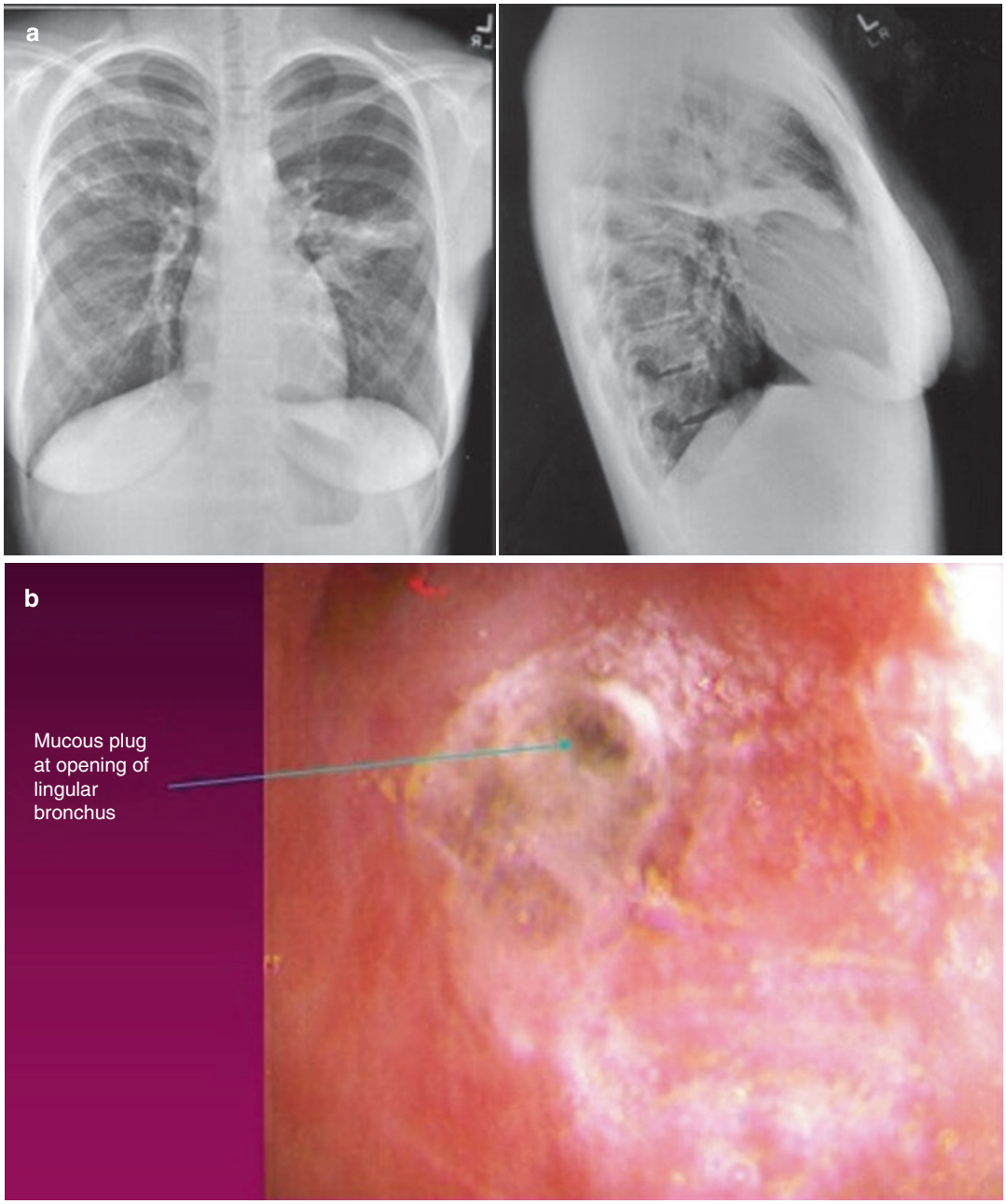

Fig. 21.10 A 15-year-old girl with ABPA and history of both asthma and CF. (**a**) Lingular segmental atelectasis in the chest films. (**b**) Mucus plug identified by aspiration to be largely eosinophilic inflammation. Corticosteroids and antifungal cleared it. (**c**) Auchterlony gel diffusion shows precipitins to *Aspergillus fumigatus*

[39–42]. Perhaps, the lack of familiarity of DPB among the physicians outside of the East Asian countries contributed to the under recognition of this entity.

Macroscopic Findings

To our knowledge, there is no report on disease-specific macroscopic finding relating to FB in DPB at present, even in adults. Two of the four

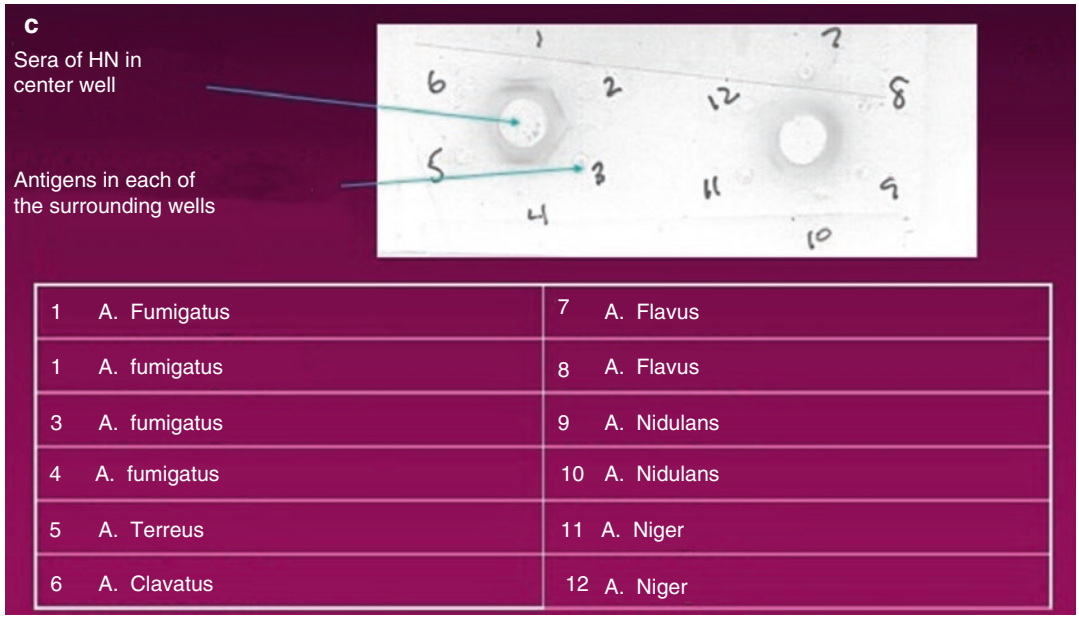

Fig. 21.10 (continued)

reported cases in children underwent FB, and secretions were seen in the bronchi [40, 41]. No other abnormality was described.

BAL Findings

BAL findings in DPB are similar to other endobronchial inflammatory disorders, in which airway neutrophilia is a key feature. An adult study comparing three biopsy-proven DPB and eight highly probable DPB patients with nine chronic bronchitis and nine normal control subjects reported that BAL neutrophil percentage was 55 ± 24.4% in DPB patients, but only 6.6 ± 6.4% in chronic bronchitis patients and 1.8 ± 1.5% in controls [101]. BAL biomarkers such as IL-8, leukotriene B4, and defensins were also reported to have higher concentration in adult patients with DPB when compared to controls [38, 102]. To date, there are no systematic published data on the cellularity or microbiological profiles in these children. The one case report of a 10-year-old boy of Korean ancestry reported lavage fluid containing 1408 neutrophils per mm^3 BAL, 393 lymphocytes/mm^3, and 485 macrophages/mm^3. Culture grew 3×10^6 cfu/ml of *Streptococcus pneumoniae* and 5×10^5 cfu/ml of *Pseudomonas aeruginosa* (personal communication, Professor Weinberger).

When Should Bronchoscopy Be Undertaken?

Although FB is a well-established and safe procedure in children [85, 103, 104], intraprocedural and post-procedural adverse events can occur [105, 106]. A study involved 333 BALs in 107 children with CF from eight centres in Australia reported that 29 BALs (8.7%) were followed by fever more than 38.5 °C and 10 (3%) had clinically significant deteriorations (five had desaturations required interventions during BAL, two required supplemental oxygen for longer than 2 hours, one tachyarrhythmia, one was hospitalized for stridor and another for central venous access malfunction) [104]. Another study from the Netherlands reported that of 66 bronchoscopies done for 48 children with CF at a median age of 8.3 years [105], complications that encountered were decreased oxygen saturation during bronchoscopy due to laryngospasm (one patient), bronchospasm (one patient), and at introduction

of rigid bronchoscopy (one patient). There were four patients desaturated after the procedure requiring oxygen supplement. Others were expiratory wheeze (one patient), fever (one patient), and nose bleed (one patient). In addition, the long-term effect of anaesthesia to the developing brain in young children, particularly of those undergoing multiple bronchoscopies, has been raised [107] but remains controversial [108]. Nevertheless, a careful consideration of which patient needs FB with conscientious estimation of its pros and cons is important so as to reduce unnecessary tests in children.

Specific to suppurative lung diseases, FB has a high yield in detecting structural and dynamic abnormalities of the tracheobronchial tree (malacia) [54, 82]. It allows direct visualization of the amount and colour of secretions as well as the mucosal appearance to assess the severity of airway inflammation macroscopically [51, 52], the hallmark of endobronchial suppuration. Furthermore, BAL can be carried out during bronchoscopy to obtain respiratory specimens for cellularity and microbiology analysis. This is of utmost importance particularly in infants and young children who are unable to expectorate. FB is indicated for these children failing to respond to conventional antimicrobial therapy [32].

The Thoracic Society of Australia and New Zealand/Australian Lung Foundation bronchiectasis guideline recommended bronchoscopy for foreign body or airway abnormalities, and to obtain specimens for culture of respiratory pathogens, including mycobacteria [109]. British Thoracic Society Guideline on non-CF bronchiectasis proposed similar recommendations, except that it was stated that for children with bronchiectasis, bronchoscopy is indicated when it affects a single lobe, to exclude a foreign body [110].

Among children with CF, some authors have advocated early or routine surveillance bronchoscopy following the diagnosis of CF [99, 111, 112], because of the high microbiology yield even in asymptomatic young children, and about 40% of new clinically relevant information with therapeutic consequences [105] and near 60% alteration in treatment after BALs [99]. Nonetheless, a Cochrane review suggested that based on a single non-blinded study involving 157 children, the routine use of BAL for the diagnosis and management of pulmonary infection in pre-school children with CF conferred no clinical benefits (lung function, nutritional parameters, or CT scan scores) compared to the standard practice (treatment based on oropharyngeal culture and clinical symptoms) [113, 114].

We summarize the indications of flexible bronchoscopy in children with endobronchial suppurative disorders in Table 21.1.

In summary, bronchoscopy on children with chronic suppuration should be assessed as case-by-case basis and remains a clinical decision. Flexible bronchoscopy is indicated when the benefits outweigh its risk and when it is the best way to obtain diagnostic information [115].

Gaps for Future Research

There are many gaps in FB relating to suppurative lung disease remain and we highlight a few below in the current context to provide insights into future preventive and therapeutic interventions.

- The yield of FB with regard to the identification of underlying aetiologies in suppurative lung disease (particularly non-CF bronchiectasis) and its contribution to the long-term outcome
- The timing of FB in the various suppurative lung disease and how it affects the treatment and future outcome
- The correlation between bronchitis severity (assessed by direct airway visualization) and microbiologic profiles in endobronchial infections, either by single pathogen or coinfections (bacterial-bacterial or viral-bacterial) and its usefulness in determining therapeutic strategies
- Standardization of airway malacia measurement for precise determination of its prevalence and impact on the disease course of endobronchial suppuration
- Revision of the current standard manner of bronchoalveolar lavage and its appropriateness in suppurative lung diseases in view of the heterogeneous distribution of lower airway pathogens and microbiota in these entities

Table 21.1 Indications for flexible bronchoscopy in disorders of endobronchial suppuration

Indication	Advantages	Precautions
Diagnostic		
1. Suspicious of structural abnormalities	Direct visualization of the airway	No standardized measurement
2. Suspicious of foreign body	Removal of distally wedged foreign body that causes bronchial obstruction	Need experienced bronchoscopist
3. Child with suboptimal clinical state, not responding to 'standard therapy'	Obtain BAL for microbiology study to guide antimicrobial therapy	Possible contamination from the upper airway
4. Recurrent PBB/newly diagnosed CSLD/bronchiectasis	Detection of underlying aetiology Assessment of inflammation and severity of bronchitis	No direct measurement tool for airway inflammation
5. Monitoring for cystic fibrosis	Early identification and eradication of pathogens in asymptomatic child	Long-term benefits are unclear
Therapeutic		
1. Persistent atelectasis due to mucus plug resistant to medical therapy	Bronchial toilet and removal of mucus plug	Increased risks of post-procedural complications (fever, hypoxaemia)
2. Bronchial obstruction due to foreign body	Removal of foreign body if not feasible with rigid bronchoscopy	Risks of bleeding, pneumothorax

References

1. Chang AB, Bush A, Grimwood K. Bronchiectasis in children: diagnosis and treatment. Lancet. 2018;392(10150):866–79.
2. Wurzel DF, Marchant JM, Clark JE, Masters IB, Yerkovich ST, Upham JW, et al. Wet cough in children: infective and inflammatory characteristics in broncho-alveolar lavage fluid. Pediatr Pulmonol. 2014;49(6):561–8.
3. Boren EJ, Teuber SS, Gershwin ME. A review of non-cystic fibrosis pediatric bronchiectasis. Clin Rev Allergy Immunol. 2008;34(2):260–73.
4. Karadag B, Karakoc F, Ersu R, Kut A, Bakac S, Dagli E. Non-cystic fibrosis bronchiectasis in children: a persisting problem in developing countries. Respiration. 2005;72(3):233–8.
5. Kapur N, Karadag B. Differences and similarities in non-cystic fibrosis bronchiectasis between developing and affluent countries. Paediatr Respir Rev. 2011;12(2):91–6.
6. Li AM, Sonnappa S, Lex C, Wong E, Zacharasiewicz A, Bush A, et al. Non-CF bronchiectasis: does knowing the aetiology lead to changes in management? Eur Respir J. 2005;26(1):8–14.
7. McCallum GB, Binks MJ. The epidemiology of chronic suppurative lung disease and bronchiectasis in children and adolescents. Front Pediatr. 2017;5:27.
8. Redding GJ. Bronchiectasis in children. Pediatr Clin N Am. 2009;56(1):157–71.
9. de Vries JJV, Chang AB, Marchant JM. Comparison of bronchoscopy and bronchoalveolar lavage findings in three types of suppurative lung disease. Pediatr Pulmonol. 2018;53(4):467–74.
10. Coleman LT, Kramer SS, Markowitz RI, Kravitz RM. Bronchiectasis in children. J Thorac Imaging. 1995;10(4):268–79.
11. Eastham KM. The need to redefine non-cystic fibrosis bronchiectasis in childhood. Thorax. 2004;59(4):324–7.
12. Gaillard EA, Carty H, Heaf D, Smyth RL. Reversible bronchial dilatation in children: comparison of serial high-resolution computer tomography scans of the lungs. Eur J Radiol. 2003;47(3):215–20.
13. Callahan CW, Redding GJ. Bronchiectasis in children: orphan disease or persistent problem? Pediatr Pulmonol. 2002;33(6):492–6.
14. King P. Pathogenesis of bronchiectasis. Paediatr Respir Rev. 2011;12(2):104–10.
15. Cole P. The damaging role of bacteria in chronic lung infection. J Antimicrob Chemother. 1997;40(S1):5–10.
16. Redding GJ, Carter ER. Chronic suppurative lung disease in children: definition and spectrum of disease. Front Pediatr. 2017;5:30.
17. Chang AB, Redding GJ, Everard ML. Chronic wet cough: protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatr Pulmonol. 2008;43(6):519–31.
18. Chang AB, Robertson CF, Van Asperen PP, Glasgow NJ, Mellis CM, Masters IB, et al. A multicenter study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest. 2012;142(4):943–50.

19. Kantar A, Chang AB, Shields MD, Marchant JM, Grimwood K, Grigg J, et al. ERS statement on protracted bacterial bronchitis in children. Eur Respir J. 2017;50(2):1602139.
20. Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and outcome of young children with chronic cough. Chest. 2006;129(5):1132–41.
21. Chang AB, Upham JW, Masters IB, Redding GR, Gibson PG, Marchant JM, et al. Protracted bacterial bronchitis: the last decade and the road ahead. Pediatr Pulmonol. 2016;51(3):225–42.
22. Wurzel DF, Marchant JM, Yerkovich ST, Upham JW, Petsky HL, Smith-Vaughan H, et al. Protracted bacterial bronchitis in children: natural history and risk factors for bronchiectasis. Chest. 2016;150(5):1101–8.
23. Chang AB, Oppenheimer JJ, Weinberger MM, Rubin BK, Grant CC, Weir K, et al. Management of children with chronic wet cough and protracted bacterial bronchitis: CHEST guideline and expert panel report. Chest. 2017;151(4):884–90.
24. Weinberger M. Tracheomalacia and protracted bacterial bronchitis resulting from straight back syndrome: a case report and commentary. Pediatr Allergy Immunol Pulmonol. 2017;30(2):116–9.
25. Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia: recent advances in diagnostics, genetics, and characterization of clinical disease. Am J Respir Crit Care Med. 2013;188(8):913–22.
26. Virginia M, Claudius W, Francesca S. Primary ciliary dyskinesia: an update on clinical aspects, genetics, diagnosis, and future treatment strategies. Front Pediatr. 2017;5:135.
27. Hosie P, Fitzgerald DA, Jaffe A, Birman CS, Morgan L. Primary ciliary dyskinesia: overlooked and undertreated in children. J Paediatr Child Health. 2014;50(12):952–8.
28. Barbato A, Frischer T, Kuehni C, Snijders D, Azevedo I, Baktai G, et al. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. Eur Respir J. 2009;34(6):1264–76.
29. Bush A, Hogg C. Primary ciliary dyskinesia: recent advances in epidemiology, diagnosis, management and relationship with the expanding spectrum of ciliopathy. Expert Rev Respir Med. 2012;6(6):663–82.
30. Goutaki M, Meier AB, Halbeisen FS, Lucas JS, Dell SD, Maurer E, et al. Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. Eur Respir J. 2016;48(4):1081–95.
31. Lucas JS, Barbato A, Collins SA, Goutaki M, Behan L, Caudri D, et al. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. Eur Respir J. 2017;49:1601090.
32. Shapiro AJ, Zariwala MA, Ferkol T, Davis SD, Sagel SD, Dell SD, et al. Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD foundation consensus recommendations based on state of the art review. Pediatr Pulmonol. 2016;51(2):115–32.
33. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519–31.
34. Castellani C, Assael BM. Cystic fibrosis: a clinical view. Cell Mol Life Sci. 2017;74(1):129–40.
35. Azuma A, Kudoh S. Diffuse panbronchiolitis in East Asia. Respirology. 2006;11(3):249–61.
36. Homma H, Yamanaka A, Tanimoto S, Tamura M, Chijimatsu Y, Kira S, et al. Diffuse panbronchiolitis: a disease of the transitional zone of the lung. Chest. 1983;83(1):63–9.
37. Kudoh S, Keicho N. Diffuse Panbronchiolitis. Clin Chest Med. 2012;33(2):297–305.
38. Poletti V, Casoni G, Chilosi M, Zompatori M. Diffuse panbronchiolitis. Eur Respir J. 2006;28(4):862.
39. Anthony M, Singham S, Soans B, Tyler G. Diffuse panbronchiolitis: not just an Asian disease: Australian case series and review of the literature. Biomed Imaging Interv J. 2009;5(4):e19.
40. Aslan AT, Ozcelik U, Talim B, Haliloglu M, Dogru D, Dalgıc F, et al. Childhood diffuse panbronchiolitis: a case report. Pediatr Pulmonol. 2005;40(4):354–7.
41. Weinberger M, Fischer A, Kao S. Diffuse panbronchiolitis in a 10-year-old boy. Pediatr Pulmonol. 2015;50(9):E32–4.
42. Zhao NN, Cao H, Zhang SS, Cao GQ. Successful treatment of diffuse panbronchiolitis in a child from Western China: a case report. Exp Ther Med. 2017;13(5):2094–6.
43. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. Am J Respir Crit Care Med. 1998;157(6 Pt 1):1829.
44. Stockley R, Bayley D, Hill S, Hill A, Crooks S, Campbell E. Assessment of airway neutrophils by sputum colour: correlation with airways inflammation. Thorax. 2001;56(5):366–72.
45. Murray MP, Pentland JL, Turnbull K, MacQuarrie S, Hill AT. Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(2):361–4.
46. Chang AB, Faoagali J, Cox NC, Marchant JM, Dean B, Petsky HL, et al. A bronchoscopic scoring system for airway secretions - airway cellularity and microbiological validation. Pediatr Pulmonol. 2006;41(9):887–92.
47. Thompson AB, Daughton D, Robbins RA, Ghafouri MA, Oehlerking M, Rennard SI. Intraluminal airway inflammation in chronic bronchitis. Am Rev Respir Dis. 1989;140(6):1527–37.
48. Thompson AB, Huerta G, Robbins RA, Sisson JH, Spurzem JR, Von Essen S, et al. The bronchitis index: a semiquantitative visual scale for the assessment of airways inflammation. Chest. 1993;103(5):1482–8.
49. De Baets F, Haerynck I, Van Daele C, Schelstraete F, De Schutter S, De Wachter E, et al. Malacia, inflammation and bronchoalveolar lavage culture in

children with persistent respiratory symptoms. Eur Respir J. 2012;39(2):392–5.
50. Smith TF, Ireland TA, Zaatari GS, Gay BB, Zwiren GT, Andrews HG. Characteristics of children with endoscopically proved chronic bronchitis. Am J Dis Child. 1985;139(10):1039–44.
51. Thomas RJ, Eg KP, Masters IB, McElrea M, Chang AB. Can a bronchoscopically defined bronchitis tool in children be validly developed? Respirology. 2108;23(S1):28.
52. Eg KP, Thomas RJ, Masters IB, McElrea M, Chang AB. Development and validation of a bronchoscopically defined bronchitis tool in children. Respirology. 2018;23(S1):168.
53. Masters IB, Chang AB. Tracheobronchomalacia in children. Expert Rev Respir Med. 2009;3(4):425–39.
54. Kompare M, Weinberger M. Protracted bacterial bronchitis in young children: association with airway malacia. J Pediatr. 2012;160(1):88–92.
55. Wurzel DF, Marchant JM, Yerkovich ST, Upham JW, Mackay IM, Masters IB, et al. Prospective characterization of protracted bacterial bronchitis in children. Chest. 2014;145(6):1271–8.
56. Goyal V, Grimwood K, Marchant JM, Masters IB, Chang AB. Paediatric chronic suppurative lung disease: clinical characteristics and outcomes. Eur J Pediatr. 2016;175(8):1077–84.
57. Fischer AJ, Singh SB, Adam RJ, Stoltz DA, Baranano CF, Kao S, et al. Tracheomalacia is associated with lower FEV1 and Pseudomonas acquisition in children with CF. Pediatr Pulmonol. 2014;49(10):960–70.
58. Boogaard R, Huijsmans SH, Pijnenburg MWH, Tiddens HAWM, de Jongste JC, Merkus PJFM. Tracheomalacia and bronchomalacia in children: incidence and patient characteristics. Chest. 2005;128(5):3391–7.
59. Kapur N, Grimwood K, Masters IB, Morris PS, Chang AB. Lower airway microbiology and cellularity in children with newly diagnosed non-CF bronchiectasis. Pediatr Pulmonol. 2012;47(3):300–7.
60. Pizzutto SJ, Grimwood K, Bauert P, Schutz KL, Yerkovich ST, Upham JW, et al. Bronchoscopy contributes to the clinical management of indigenous children newly diagnosed with bronchiectasis. Pediatr Pulmonol. 2013;48(1):67–73.
61. Ratjen F, Waters V, Klingel M, McDonald N, Dell S, Leahy TR, et al. Changes in airway inflammation during pulmonary exacerbations in patients with cystic fibrosis and primary ciliary dyskinesia. Eur Respir J. 2016;47(3):829–36.
62. Marchant JM, Gibson PG, Grissell TV, Timmins NL, Masters IB, Chang AB. Prospective assessment of protracted bacterial bronchitis: airway inflammation and innate immune activation. Pediatr Pulmonol. 2008;43(11):1092–9.
63. Cohen-Cymberknoh M, Kerem E, Ferkol T, Elizur A. Airway inflammation in cystic fibrosis: molecular mechanisms and clinical implications. Thorax. 2013;68:1157–62.
64. Hilliard TN, Regamey N, Shute JK, Nicholson AG, Alton EWFW, Bush A, et al. Airway remodelling in children with cystic fibrosis. Thorax. 2007;62(12):1074.
65. Gilchrist FJ, Salamat S, Clayton S, Peach J, Alexander J, Lenney W. Bronchoalveolar lavage in children with cystic fibrosis: how many lobes should be sampled? Arch Dis Child. 2011;96(3):215–7.
66. Narang R, Bakewell K, Peach J, Clayton S, Samuels M, Alexander J, et al. Bacterial distribution in the lungs of children with protracted bacterial bronchitis. PLoS One. 2014;9(9):e108523.
67. Gutierrez JP, Grimwood K, Armstrong DS, Carlin JB, Carzino R, Olinsky A, et al. Interlobar differences in bronchoalveolar lavage fluid from children with cystic fibrosis. Eur Respir J. 2001;17(2):281–6.
68. Hare KM, Pizzutto SJ, Chang AB, Smith-Vaughan HC, McCallum GB, Beissbarth J, et al. Defining lower airway bacterial infection in children with chronic endobronchial disorders. Pediatr Pulmonol. 2018;53(2):224–32.
69. Hare KM, Grimwood K, Leach AJ, Smith-Vaughan H, Torzillo PJ, Morris PS, et al. Respiratory bacterial pathogens in the nasopharynx and lower airways of Australian indigenous children with bronchiectasis. J Pediatr. 2010;157(6):1001–5.
70. Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phenlan PD. Bronchoalveolar lavage or oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. Pediatr Pulmonol. 1996;21(5):267–75.
71. Emiralioglu N, Sancak B, Tugcu GD, Sener B, Yalcın E, Dogru D, et al. Comparison of bronchoalveolar lavage and sputum microbiology in patients with primary ciliary dyskinesia. Pediatr Allergy Immunol Pulmonol. 2017;30(1):14–7.
72. Blau H, Linnane B, Carzino R, Tannenbaum E-L, Skoric B, Robinson PJ, et al. Induced sputum compared to bronchoalveolar lavage in young, non-expectorating cystic fibrosis children. J Cyst Fibros. 2014;13(1):106–10.
73. Kapur N, Masters IB, Chang AB. Exacerbations in non-cystic fibrosis bronchiectasis: clinical features and investigations. Respir Med. 2009;103:1681–7.
74. Hare KM, Smith-Vaughan HC, Leach AJ, Pizzutto SJ, McCallum GB, Chang AB. Reduced nontypeable Haemophilus influenzae lower airway infection in children with chronic endobronchial suppuration vaccinated with the 10-valent pneumococcal H. influenzae protein D conjugate vaccine. Vaccine. 2018;36(13):1736–42.
75. Hare KM, Smith-Vaughan HC, Chang AB, Pizzutto S, Petsky HL, McCallum GB, et al. Propensity of pneumococcal carriage serotypes to infect the lower airways of children with chronic endobronchial infections. Vaccine. 2017;35(5):747–56.
76. Van Der Gast CJ, Cuthbertson L, Rogers GB, Pope C, Marsh RL, Redding GJ, et al. Three clinically distinct chronic pediatric airway infections share

a common core microbiota. Ann Am Thorac Soc. 2014;11(7):1039–48.
77. Hall-Stoodley L, Stoodley P. Evolving concepts in biofilm infections. Cell Microbiol. 2009;11(7):1034–43.
78. Starner T, Zhang N, Kim G, Apicella M, McCray P. Haemophilus influenzae forms biofilms on airway epithelia: implications in cystic fibrosis. Am J Respir Crit Care Med. 2006;174(2):213–20.
79. Bjarnsholt T, Jensen PØ, Fiandaca MJ, Pedersen J, Hansen CR, Andersen CB, et al. Pseudomonas aeruginosa biofilms in the respiratory tract of cystic fibrosis patients. Pediatr Pulmonol. 2009;44(6):547–58.
80. Marsh RL, Thornton RB, Smith-Vaughan HC, Richmond P, Pizzutto SJ, Chang AB. Detection of biofilm in bronchoalveolar lavage from children with non-cystic fibrosis bronchiectasis. Pediatr Pulmonol. 2015;50:284–92.
81. de Blic J, Midulla F, Barbato A, Clement A, Dab I, Eber E, et al. Bronchoalveolar lavage in children. ERS task force on bronchoalveolar lavage in children. European Respiratory Society. Eur Respir J. 2000;15(1):217–31.
82. Chang AB, Boyce NC, Masters IB, Torzillo PJ, Masel JP. Bronchoscopic findings in children with non-cystic fibrosis chronic suppurative lung disease. Thorax. 2002;57(11):935–8.
83. Douros K, Alexopoulou E, Nicopoulou A, Anthracopoulos MB, Fretzayas A, Yiallouros P, et al. Bronchoscopic and high-resolution CT scan findings in children with chronic wet cough. Chest. 2011;140(2):317–23.
84. Zgherea D, Pagala S, Mendiratta M, Marcus MG, Shelov SP, Kazachkov M. Bronchoscopic findings in children with chronic wet cough. Pediatrics. 2012;129(2):e364–9.
85. Terkawi RS, Altirkawi KA, Terkawi AS, Mukhtar G, Al-Shamrani A. Flexible bronchoscopy in children: utility and complications. Int J Pediatr Adolesc Med. 2016;3(1):18–27.
86. Ciftci AO, Bingöl-Koloğlu M, Şenocak ME, Tanyel FC, Büyükpamukçu N. Bronchoscopy for evaluation of foreign body aspiration in children. J Pediatr Surg. 2003;38(8):1170–6.
87. Narang R, Bakewell K, Peach J, Clayton S, Samuels M, Alexander J, et al. Is bronchoscopy needed in children with persistent bacterial bronchitis? Thorax. 2013;68(S3):A40.
88. Emiralioglu N, Kiper N, Yalçin E, Dogru Ersöz D, Özçelik U. Flexible bronchoscopy findings in children with protracted bacterial bronchitis. Eur Respir J. 2015;46(S59):PA1351.
89. Settipane GA. Epidemiology of nasal polyps. Allergy Asthma Proc. 1996;17(5):231–6.
90. Brown DE, Pittman JE, Leigh MW, Fordham L, Davis SD. Early lung disease in young children with primary ciliary dyskinesia. Pediatr Pulmonol. 2008;43(5):514–6.
91. Chang H, Adjemian J, Dell SD, Ferkol TW, Leigh MW, Milla CE, et al. Prevalence of airway microbial flora in primary ciliary dyskinesia. Am J Respir Crit Care Med. 2015;191:A1798.
92. McLaughlin AM, McGrath E, Barry R, Egan JJ, Gallagher CG. Treatment of lobar atelectasis with bronchoscopically administered recombinant human deoxyribonuclease in cystic fibrosis? Clin Respir J. 2008;2(2):123–6.
93. de Almeida MB, Bussamra MHF, Rodrigues JC. Allergic bronchopulmonary aspergillosis in paediatric cystic fibrosis patients. Paediatr Respir Rev. 2006;7(1):67–72.
94. Mastella G, Rainisio M, Harms HK, Hodson ME, Koch C, Navarro J, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis. A European epidemiological study. Eur Respir J. 2000;16(3):464–71.
95. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clin Exp Allergy. 2013;43(8):850–73.
96. Colin AA, Tsiligiannis T, Nosé V, Waltz DA. Membranous obliterative bronchitis: a proposed unifying model. Pediatr Pulmonol. 2006;41(2):126–32.
97. Regamey N, Tsartsali L, Hilliard TN, Fuchs O, Tan H-L, Zhu J, et al. Distinct patterns of inflammation in the airway lumen and bronchial mucosa of children with cystic fibrosis. Thorax. 2012;67(2):164.
98. Laguna T, Wagner B, Williams C, Stevens M, Robertson C, Welchlin C, et al. Airway microbiota in bronchoalveolar lavage fluid from clinically well infants with cystic fibrosis. PLoS One. 2016;11(12):e0167649.
99. Linnane B, Vaish S, Clarke D, O'Sullivan N, McNally P. The findings of a clinical surveillance bronchoalveolar lavage programme in pre-school patients with cystic fibrosis. Pediatr Pulmonol. 2015;50(4):327–32.
100. Paul L. Is bronchoscopy an obsolete tool in cystic fibrosis? The role of bronchoscopy in cystic fibrosis and its clinical use. J Thorac Dis. 2017;9(S10):S1139–45.
101. Ichikawa Y, Koga H, Tanaka M, Nakamura M, Tokunaga N, Kaji M. Neutrophilia in bronchoalveolar lavage fluid of diffuse panbronchiolitis. Chest. 1990;98(4):917–23.
102. Hiratsuka T, Mukae H, Iiboshi H, Ashitani J, Nabeshima K, Minematsu T, et al. Increased concentrations of human [beta]-defensins in plasma and bronchoalveolar lavage fluid of patients with diffuse panbronchiolitis. Thorax. 2003;58(5):425.
103. Carlens J, Fuge J, Price T, Deluca DS, Price M, Hansen G, et al. Complications and risk factors in pediatric bronchoscopy in a tertiary pediatric respiratory center. Pediatr Pulmonol. 2018;53(5):619–27.
104. Wainwright CE, Grimwood K, Carlin JB, Vidmar S, Cooper PJ, Francis PW, et al. Safety of bronchoal-

veolar lavage in young children with cystic fibrosis. Pediatr Pulmonol. 2008;43(10):965–72.
105. Boogaard R, de Jongste JC, Lequin MH, Devos AS, Tiddens HAWM, Merkus PJFM. Yield from flexible bronchoscopy in pediatric cystic fibrosis patients. J Bronchol. 2008;15(4):240–6.
106. Soyer T. The role bronchoscopy in the diagnosis of airway disease in children. J Thorac Dis. 2016;8(11):3420–6.
107. Olsen AE, Brambrink MA. Anesthesia for the young child undergoing ambulatory procedures: current concerns regarding harm to the developing brain. Curr Opin Anaesthesiol. 2013;26(6):677–84.
108. Clausen NG, Kähler S, Hansen TG. Systematic review of the neurocognitive outcomes used in studies of paediatric anaesthesia neurotoxicity. Br J Anaesth. 2018;120(6):1255–73.
109. Chang AB, Bell SC, Byrnes CA, Grimwood K, Holmes PW, King PT, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand. Med J Aust. 2010;193(6):356–65.
110. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. Thorax. 2010;65(S1):i1–58.
111. Hilliard TN, Sukhani S, Francis J, Madden N, Rosenthal M, Balfour-Lynn I, et al. Bronchoscopy following diagnosis with cystic fibrosis. Arch Dis Child. 2007;92(10):898–9.
112. Stafler P, Davies JC, Balfour-Lynn IM, Rosenthal M, Bush A. Bronchoscopy in cystic fibrosis infants diagnosed by newborn screening. Pediatr Pulmonol. 2011;46(7):696–700.
113. Jain K, Wainwright C, Smyth AR. Bronchoscopy-guided antimicrobial therapy for cystic fibrosis. Cochrane Database Syst Rev. 2013;12:CD009530-CD.
114. Wainwright CE, Vidmar S, Armstrong DS, Byrnes CA, Carlin JB, Cheney J, et al. Effect of bronchoalveolar lavage–directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis: a randomized trial. JAMA. 2011;306(2):163–71.
115. Midulla F, de Blic J, Barbato A, Bush A, Eber E, Kotecha S, et al. Flexible endoscopy of paediatric airways. Eur Respir J. 2003;22(4):698–708.

Aspiration

22

Gregory Burg and Dan Benscoter

Introduction

Aspiration is the penetration of any material beyond the subglottic airway and into the trachea or bronchi. Aspiration can occur as an acute event or as a chronic ongoing or recurrent process. The sequela of aspiration depends primarily on the character, volume, and chronicity of material aspirated. Acute aspiration of large volume, obstructive, or toxic material can rapidly progress to respiratory distress or failure.

Acutely aspirated solid material that obstructs the trachea and large bronchi can quickly impair gas exchange and may require emergent intervention with rigid or flexible bronchoscopy for foreign body removal to obviate the need for extracorporeal membrane oxygenation (ECMO) [1–3]. A single event of aspiration of large volume, nonsolid material such as swimming pool water or blood, likewise can cause acute respiratory failure requiring advanced life support with intubation and mechanical ventilation or ECMO support. Furthermore, an acute aspiration event of even small volumes of toxic material, such as hydrocarbon, can cause a rapidly progressive acute pneumonitis with respiratory failure via airway mucosal edema and inflammation, airway obstruction, and injury to terminal respiratory units resulting in pulmonary edema and an ARDS-like syndrome [1–3]. Acute aspiration events cannot only lead to rapid respiratory distress and failure, but can also cause significant airway injury with resultant long-term implications [4, 5].

Chronic pulmonary aspiration, although common in pediatrics, can be difficult to diagnose. Children with chronic aspiration may have symptoms that are mistaken for other respiratory disorders such as asthma. The prevalence of pulmonary aspiration in children is unknown, as it is a heterogeneous disorder with no clear gold standard for diagnosis. Repetitive passage of upper airway secretions or saliva, food or drink, refluxed gastric contents, or a combination of the aforementioned materials, defines chronic pulmonary aspiration. Aspiration results from the inability to protect the airway and becomes clinically relevant when it occurs sufficiently enough to cause chronic or recurring respiratory symptoms or lung disease. Aspiration typically occurs intermittently, but may be nearly continuous depending on the underlying cause of the aspiration.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_22

Protecting the airway is a complex process that depends on the integration and coordination of swallowing and breathing through a shared aerodigestive tract [6–8]. Aspiration may result if there are disruptions in the neurologic, anatomic, or functional components of this complex coordinated effort.

Advances in the care and improved survival rates of critically ill, often premature, neonates over the past few decades have resulted in an increased number of medically complex infants and children [3, 6–17]. These children are at higher risk for aspiration secondary to multiple problems arising from either the underlying condition or the ensuing management. This has led to the development of the aerodigestive model – an interdisciplinary team of otolaryngologists, pulmonologists, gastroenterologists, general surgeons, anesthesiologists, and speech and language pathologists as well as radiologists, neonatologists, geneticists, behavioral health specialists, social workers, nurse practitioners, physician assistants, nurses, respiratory therapists, sleep medicine specialists, and general pediatricians coordinating care for these complex patients [17, 18]. Patients with aerodigestive disorders have multiple, often overlapping, medical problems including anatomic airway pathology, tracheostomy dependence, primary pulmonary disease, neurologic impairment, feeding and gastrointestinal disease, and sleep disorders. A coordinated, proactive approach to these patients allows for the development of an efficient plan for diagnostic testing and multidisciplinary evaluation that reduces the burden on the patients and their families. Commonly, these children are born very prematurely or have congenital syndromes which predispose them to aspiration. It can often be difficult to distinguish between the symptoms of chronic aspiration and other underlying conditions, such as asthma, bronchopulmonary dysplasia, or tracheobronchomalacia.

The downstream effect of chronic pulmonary aspiration can result in significant morbidity for children. Children with chronic pulmonary aspiration may be repetitively hospitalized for aspiration pneumonia. Repeated insults to the lungs can result in the development of progressive lung injury and bronchiectasis, which can ultimately lead to respiratory failure [1–5, 17]. In children with neurologic impairment or congenital syndromes associated with aspiration, chronic pulmonary aspiration is a leading cause of death. There is often a delay in the diagnosis of chronic pulmonary aspiration in children without neurologic impairment who are frequently treated inappropriately and ineffectively for asthma due to symptoms of wheezing and chronic cough. This delay in diagnosis and management can result in chronic lung disease and the development of bronchiectasis.

The diagnosis of chronic pulmonary aspiration is challenging, as there is no gold-standard diagnostic test. Some nocturnal aspiration of saliva and gastroesophageal reflux material occurs in normal healthy subjects [19]. In others, more significant chronic aspiration can result in progressive lung injury and disease. The threshold at which pathologic aspiration occurs likely varies between individuals. Histopathologically, patients with chronic pulmonary aspiration develop bronchiolocentric inflammation with giant cells, increased peribronchiolar and perivascular lymphocytes, and may have identifiable food or vegetative matter [4, 20–22]. Radiographically this corresponds with bronchiolar obstruction and injury on high-resolution chest computed tomography (CT), as demonstrated by centrilobular "tree-in-bud" opacities and bronchiectasis, though these radiographic findings are not specific, nor diagnostic, for chronic aspiration [2, 5, 22, 23].

Swallowing

Swallowing is a highly complex process reliant on intact anatomy and coordinated sensory and motor function with both voluntary and involuntary actions [8]. The initial oral phase is characterized by chewing and sucking of ingested food to prepare a bolus which is then pushed into the pharynx in a voluntary maneuver. Following delivery of the bolus, airway protection during swallowing depends on involuntary mechanisms. This process involves cessation of breathing,

closure of the true vocal cords, and contraction of the intrinsic laryngeal muscles. Elevation of the laryngeal structures causes opening of the cricopharyngeus and contraction of the pharyngeal constrictors results in movement of the bolus past the upper esophageal sphincter, where the bolus is then transported to the stomach via peristalsis. The larynx subsequently returns to the resting position and respiration continues through an open airway.

Development of Swallowing

The development of sucking and swallowing begins in the early stages of fetal development [7, 8, 24–26]. The anatomy of the oropharynx, larynx, trachea, and esophagus results from growth and development early after fertilization and continues after birth. Normal swallowing relies on a complex intact and coordinated neuronal network. At 18–24 weeks gestation, myelination of the roots of cranial nerves has occurred, corresponding with the opening and closing of the jaw, anterior tongue movements, and suckling which can be seen on ultrasound as early as 18 weeks gestation. The oropharynx has one of the most diverse sensory inputs of the entire body with a range of afferent modalities including taste, two-point discrimination, vibrotactile detection, proprioception, nociception, and thermal sensitivity. These cortical inputs prompt initiation of the voluntary oral phase of swallowing. By 26–29 weeks gestation, reflexes between taste buds and facial muscles are present and nonnutritive sucking is observed. Full oral nutrition and hydration can typically be accomplished at 34 weeks gestation and may be accomplished as early as 32–33 weeks gestation in some infants. Swallowing continues to mature beyond term.

Pathophysiology of Aspiration

Any breakdown in anatomic structure and function or coordination of swallowing can lead to failure to protect against aspiration. If there is a delay in the initiation of swallowing as the food bolus is prepared in the mouth, the bolus can enter the pharynx early, before the protective actions of the pharyngeal phase occur. Early delivery of the bolus to the pharynx can leave the laryngeal inlet susceptible to penetration and aspiration. Inadequate laryngeal elevation may result in the food bolus passing close to the posterior larynx. Delay in opening of the upper esophageal sphincter may allow the bolus to persist in the hypopharynx for an extended period of time, which creates the potential for overflowing to the glottis similar to what may occur with regurgitation of food. These mechanisms also occur at the level at which a laryngeal cleft can place the airway at risk for aspiration.

During swallowing, the protection of the airway is dependent upon the actions of the intrinsic laryngeal muscles, which are innervated by the superior laryngeal nerve and the recurrent laryngeal nerve. The intrinsic laryngeal muscles act in a coordinated fashion to open and close the supraglottic airway during swallowing. This area of the airway has a high concentration of sensory inputs, including mechanical, chemical, and thermal receptors. There is wide variability in the sensitivity and response of these receptor types in different developmental stages and pathologic states. It has been well demonstrated that impaired laryngeal sensation correlates highly with aspiration [27–29]. The cough response is usually not present at birth and develops during infancy [30].

There are certain patient populations that are at higher risk for chronic pulmonary aspiration due to swallowing dysfunction. General conditions responsible for chronic pulmonary aspiration may include central or peripheral neurologic disease, anatomic abnormalities, or functional disorders (Table 22.1). There are many genetic diseases that have a strong predisposition to aspiration. In some children, there may be no identifiable disorder despite the presence of pulmonary aspiration resulting in chronic respiratory symptoms or development of lung disease. When no etiology for aspiration is identified, the dysphagia is most often due to delayed initiation of swallowing, which will typically resolve by 3 years of age.

Table 22.1 Conditions associated with chronic pulmonary aspiration

Neurologic disorders:
Depressed consciousness
Static or progressive encephalopathy
Traumatic brain injury
Stroke/cerebrovascular accident
Hydrocephalus
Brain tumors
Leukodystrophy
Cerebral palsy
Arnold–Chiari malformation
Muscular dystrophy
Congenital myopathy
Spinal muscle atrophy
Guillain–Barré syndrome
Myasthenia gravis
Anatomic abnormalities:
Choanal stenosis or atresia
Cleft palate
Pharyngeal stenosis
Macroglossia
Laryngeal/pharyngeal tumors
Vascular malformation
Upper airway trauma
Laryngomalacia
Laryngeal web
Laryngeal cleft
Vocal cord paralysis
Subglottic stenosis
Tracheoesophageal fistula
Tracheostomy
Esophageal atresia
Esophageal stricture
Vascular ring
Tracheal stenosis
Congenital syndromes, sequences, and associations:
CHARGE syndrome
Moebius syndrome
Cornelia de Lange syndrome
Coffin–Siris syndrome
Smith–Lemli–Opitz syndrome
Trisomy 18
Trisomy 21
Velocardiofacial syndrome
Cri du chat syndrome
Pierre–Robin sequence
VACTERL association
Gastrointestinal disorders:
Gastroesophageal reflux
Esophageal dysmotility
Gastrointestinal foreign body
Cricopharyngeal achalasia
Gastroparesis
Prematurity

An association between gastroesophageal reflux and respiratory symptoms, namely chronic cough, wheezing, apnea, and recurrent lung infections has been well documented [31–34]. Attributing respiratory symptoms of chronic pulmonary aspiration to gastroesophageal reflux disease is difficult [35–40]. Several studies have shown a causal relationship between gastroesophageal reflux disease and chronic pulmonary aspiration [34, 41–44]. Aspiration of gastric contents into the lungs has been shown to cause damage to the alveoli, acute neutrophilic inflammation, and desquamation of the mucosa [45]. An animal model study has shown that pulmonary aspiration of acidic content causes an immediate inflammatory response and pneumonitis regardless of whether the material was strongly or weakly acidic [46]. There are other components present in aspirated gastric content, including pepsin, bowel acids, and food particulate matter, all of which can impose lung injury. Animal models for chronic pulmonary aspiration have demonstrated that the presence of food particulate matter was the strongest predictor of histopathologic changes and that the acidity of the aspirated material had no significant effect on chronic histology [47, 48].

Evaluation of Aspiration

Given the significant morbidity conferred by chronic pulmonary aspiration, efforts should be made to determine the underlying cause of aspiration and extent of lung injury in order to reduce the risk of evolving lung disease. Although there is no gold standard for the diagnosis of chronic pulmonary aspiration, various studies can provide supporting evidence for the presence and etiology of chronic aspiration.

Chest Imaging

Chest imaging may be performed to evaluate for evidence of lung disease consistent with pulmonary aspiration. The chest radiograph may reveal nonspecific findings related to early lung injury due to chronic aspiration, including peribronchial thickening or segmental or sub-segmental atelectasis. In severe cases, evidence for bronchiectasis can be noted on the chest radiograph as the "tram track" sign, a set of parallel lines on the radiograph corresponding with dilated peripheral bronchi. In general, the chest radiograph lacks the sensitivity to detect early evidence of bronchiectasis.

The high-resolution chest CT (HRCT) is a more sensitive tool to evaluate for lung disease due to aspiration. Findings on HRCT may include tree-in-bud opacities, ground-glass opacities, atelectasis, or bronchial wall thickening. Air-trapping may be readily seen if the HRCT is performed with inspiratory and expiratory images. Obtaining adequate images may require sedation in young children who are unable to follow directions or perform a breath hold during the study [49, 50]. The HRCT is the gold standard for detecting bronchiectasis, which may develop in children with severe or long-standing aspiration (Fig. 22.1). The degree of bronchiectasis can be described by the Reid classification: cylindrical, varicose, and cystic bronchiectasis [51]. The most common locations for aspiration lung injury include the right upper lobe, right lower lobe, and left lower lobe [5]. While the finding of bronchiectasis has long been thought to represent irreversible lung damage, more recently it has been shown that early bronchiectasis may be reversible [52].

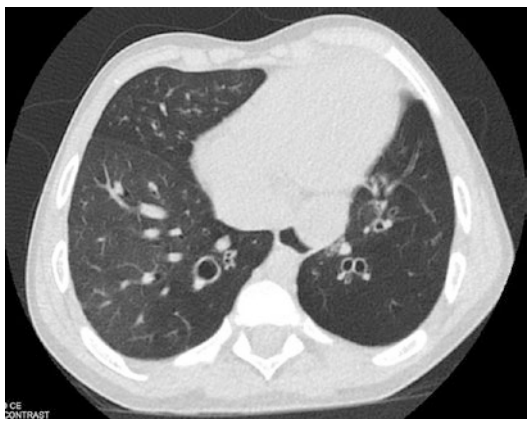

Fig. 22.1 High-resolution chest computed tomography (HRCT) of a 15-year-old boy with CHARGE association with chronic pulmonary aspiration revealing bronchiectasis in the bilateral lower lobes

Oral Motor Feeding Assessment

A clinical assessment by a skilled speech and language pathologist (SLP) or occupational therapist can be a valuable tool for evaluating the child with dysphagia and suspected pulmonary aspiration. The oral motor feeding assessment involves a detailed history, an assessment of oral structures and function, as well as an observation of oral sensorimotor skills during feeding [53]. The clinical evaluation may have high sensitivity for detecting aspiration of liquids, but may be less sensitive for detecting aspiration of solids [54].

Videofluoroscopic Swallow Study

The videofluoroscopic swallow study (VSS), or modified barium swallow study, is a useful tool to evaluate the risk of aspiration with oral intake for children who will actively take food or drink by mouth. When performed in the presence of an experienced SLP or occupational therapist, the VSS can inform the team of the child's swallowing mechanics and safety in swallowing different consistencies. The VSS uses standardized commercial contrast materials or mixes standard barium contrast with thin or thickened liquids, purees, or solid foods and uses fluoroscopy to evaluate the oral, pharyngeal, and esophageal phases of swallowing. The primary drawback of the VSS is that the study relies on active participation from the patient. If the child is unable or unwilling to eat or drink, the sensitivity of the study to detect aspiration can be markedly reduced.

Functional Endoscopic Evaluation of Swallowing

The functional endoscopic evaluation of swallowing (FEES) can be performed by any provider skilled in bedside endoscopy of the upper airway. During the FEES, the laryngeal structures are visualized while the patient swallows different consistencies of solids or liquids [55]. Comparison of the VSS with FEES has shown strong agreement in the evaluation of swallowing function [56, 57]. One benefit of the FEES is that the study allows for the observation of oral secretion management and can help determine the risk for salivary aspiration. As such, FEES can be performed on children who are unable to eat or drink by mouth.

Dye Testing

In children with tracheostomy tubes, several drops of green food dye can be mixed into food or drink or instilled into the oropharynx [58]. Suctioning dye-stained secretions from the tracheostomy tube indicates that aspiration has occurred to some degree. Dye testing does not help determine the mechanism of aspiration and may need to be repeated several times before evidence of aspiration is noted as the reported sensitivity for detecting pulmonary aspiration is highly variable [59].

Rigid Bronchoscopy

Rigid bronchoscopy is a critical part of the evaluation of aspiration for any child. Rigid bronchoscopy allows for visualization of the posterior larynx and manipulation of laryngeal structures. Rigid bronchoscopy is the gold standard for the diagnosis of a laryngeal cleft and is well equipped to identify cricopharyngeal achalasia. The rigid bronchoscope is also well suited to evaluate the trachealis when searching for an H-type tracheoesophageal fistula.

Esophageal Impedance

A 24-hour esophageal impedance study may help to define the degree of antegrade and retrograde flow within the esophagus for children with suspected gastroesophageal reflux contributing to respiratory symptoms, including symptoms of pulmonary aspiration [60]. While the presence of gastroesophageal reflux does not necessarily confer an increased risk for aspiration, any episodes of gastroesophageal reflux detected to extend above the upper esophageal sphincter may be considered opportunities for aspiration.

Other Studies

Many other diagnostic studies may be indicated during the evaluation of the etiology of chronic pulmonary aspiration. Magnetic resonance imaging (MRI) of the brain may be indicated when there is a suspected neurologic cause for aspiration or if there is no identifiable anatomic abnormality to explain a child's aspiration [61]. Esophageal manometry or high-resolution manometry may be performed to evaluate esophageal motility. An esophagram or upper gastrointestinal (GI) series may be completed to assess the structure and function of the upper GI tract. Endoscopy of the upper GI tract is a key part of the aerodigestive evaluation to evaluate for structural and inflammatory abnormalities of the upper GI tract. Nuclear medicine studies can be considered to evaluate for salivary aspiration.

Flexible Bronchoscopy

There are several indications for performing flexible bronchoscopy for the child with pulmonary aspiration: (1) definition of upper and lower airway structural and dynamic abnormalities, (2) evaluation of secretion burden and degree of inflammation of the upper and lower airway, and (3) obtaining bronchoalveolar lavage specimen for diagnostic purposes. In the event of an acute

aspiration event, flexible bronchoscopy may also be indicated for therapeutic clearance of lower airway secretions or aspirated food particulate or gastric contents. Although aspiration of gastric contents is a rare event during anesthesia, flexible bronchoscopy may be useful to clear the lower airways and check for residual debris following initial stabilization and management of the airway by the anesthesiologist [62].

For the child with chronic aspiration, thoughtful consideration should be given as to how flexible bronchoscopy is performed. A full evaluation of the upper airway is often useful in children with chronic pulmonary aspiration; however, prolonged evaluation of the upper airway could place the child at risk for aspiration of oral secretions before the lower airways are evaluated. Careful suctioning of upper airway secretions prior to flexible bronchoscopy can help minimize the risk of salivary aspiration. Upon application of topical lidocaine to the vocal cords, any residual saliva may be easily aspirated, potentially clouding the interpretation of the lower airway evaluation. In some cases, saliva can be visualized coursing down the trachea during flexible bronchoscopy (Fig. 22.2). Preemptive intubation with a cuffed endotracheal tube can be considered if a detailed assessment of the lower airway secretion burden is critical to either diagnosing aspiration or making decisions about subsequent management. This would also allow the bronchoscopist to obtain bronchoalveolar lavage specimen with minimal risk for contamination of the lower airways with saliva during induction of anesthesia.

Upper Airway Evaluation

Careful evaluation of the upper airway should be performed in children with pulmonary aspiration, especially if there are symptoms of upper airway obstruction [63]. Young children with upper airway obstruction may have difficulty coordinating breathing and swallowing, and surgical interventions to relieve obstruction may reduce the risk of chronic pulmonary aspiration. Assessment of the upper airway may be performed under drug-induced sleep endoscopy (DISE) conditions; however, prolonged evaluation of the upper airway may confer some risk for salivary aspiration during the procedure. Placement of an artificial airway may reduce the risk of aspiration during the procedure; however, this may severely limit the ability to fully evaluate upper airway anatomy and dynamics. If the trans-nasal approach is taken, it may be prudent to suction the upper airway and rapidly evaluate the lower airways once topical lidocaine is applied to reduce the risk of contamination of the lower airways prior to performing bronchoalveolar lavage.

In some cases, documentation of the secretion burden in the upper airway may be beneficial. For children with sialorrhea who are at risk for salivary aspiration, visualization of copious secretions in the hypopharynx or saliva coating the laryngeal structures may be helpful in convincing parents of the risk for salivary aspiration. As flexible bronchoscopy is performed under artificial conditions, awake upper airway endoscopy or FEES may be more effective in demonstrating pooling of secretions and consequent aspiration risk to caregivers. The degree of laryngeal edema and inflammation should be noted, although this finding is nonspecific and may not correlate with the presence of gastroesophageal reflux [64].

Evaluation for Laryngeal Cleft

Rigid bronchoscopy is considered the gold standard for the diagnosis of a laryngeal cleft. In some cases, a laryngeal cleft can be noted on flexible bronchoscopy; however, the inability to fully expose the laryngeal structures and manipulate tissue makes flexible bronchoscopy prone to missing the diagnosis of the cleft. In the absence of rigid bronchoscopy, the yield for diagnosing a laryngeal cleft with flexible bronchoscopy can be increased by visualizing the supraglottic structures while a laryngoscope blade is inserted to the level of the vocal cords or through the glottis to

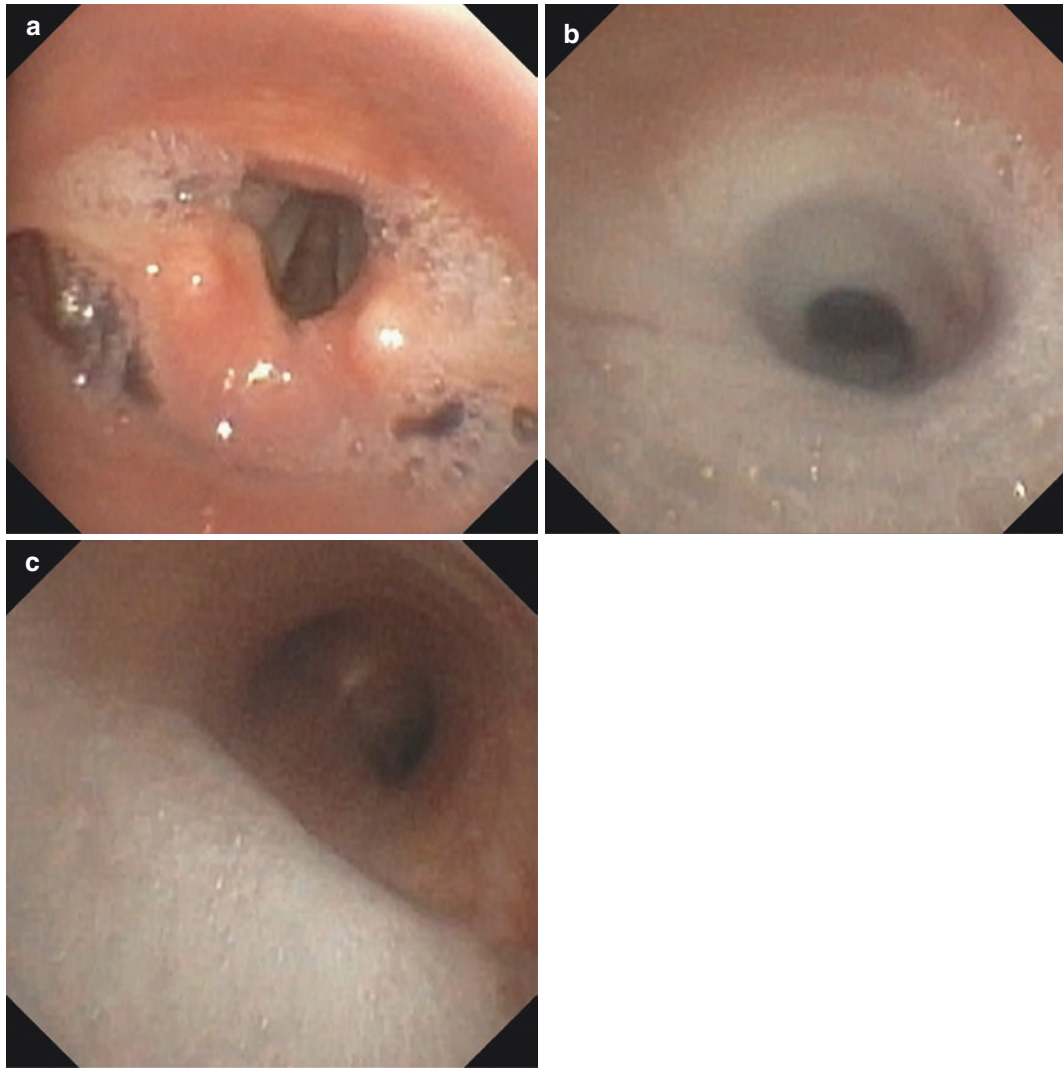

Fig. 22.2 Saliva aspirated during flexible bronchoscopy: (**a**) Copious upper airway secretions coating laryngeal structures. (**b**) Saliva present in the cervical trachea obscuring the view of tracheal mucosa. (**c**) Wall of saliva ending in the distal trachea, beyond which normal trachea and mainstem bronchi are visualized

adequately spread the arytenoids (Fig. 22.3). While this technique may increase the sensitivity for diagnosing a laryngeal cleft, the presence of a cleft should not be excluded without rigid bronchoscopy [65].

Vocal Cord Paralysis

Flexible bronchoscopy is inadequate for diagnosis of vocal cord paralysis or vocal cord paresis when performed under general anesthesia, even when the patient is spontaneously breathing. While normal bilateral vocal fold movement may be reassuring, the absence of normal vocal fold mobility or the presence of only unilateral vocal fold mobility must be confirmed when the patient is awake. Other structural abnormalities such as vocal fold atrophy or a posterior glottis scar band may raise suspicion for vocal cord paralysis or paresis; however, awake upper airway endoscopy or FEES would be the preferred method of diagnosis of aspiration due to vocal fold immobility.

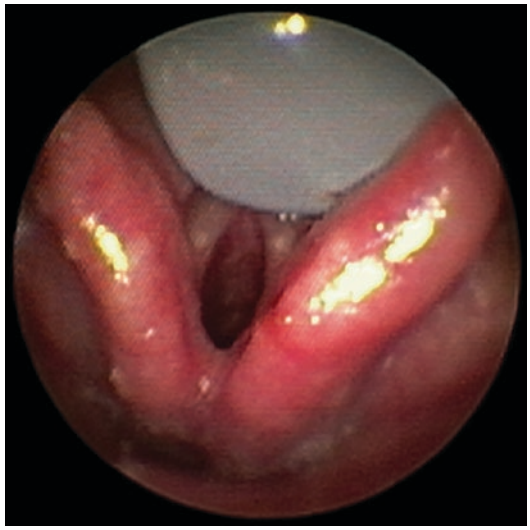

Fig. 22.3 Evaluation for laryngeal cleft. A laryngoscope blade is inserted to the level of the vocal cords, separating the arytenoids and revealing the presence of a type 2 laryngeal cleft

Lower Airway Abnormalities

Full evaluation of the lower airways for anatomic abnormalities contributing to chronic pulmonary aspiration is a critical piece of the evaluation. Lower airway anatomic and dynamic obstruction may increase the risk for aspiration. Tracheomalacia associated with repaired tracheoesophageal fistula may help to explain the quality of a cough in a patient with concern for ongoing aspiration [66]. Careful evaluation of the trachealis should be performed to rule out the presence of a tracheoesophageal fistula. Recurrent and secondary tracheoesophageal fistulae have been reported in patients with a history of repaired tracheoesophageal fistula [67]. While rigid bronchoscopy has many advantages in the evaluation of the trachealis, a fistula can be identified with a thorough examination with flexible bronchoscopy. Simultaneous evaluation with flexible bronchoscopy and esophagoscopy with insufflation of the esophagus may help identify a small or difficult to locate H-type fistula. Likewise, intubation of the esophagus with a cuffed endotracheal tube may help identify a fistula if the trachealis is closely examined while positive pressure is applied through the endotracheal tube as long as the end of the tube is above the suspected fistula site. A more detailed discussion of identification and endoscopic management of the tracheoesophageal fistula is provided in Chap. 31.

Less common than the tracheoesophageal fistula, a bronchoesophageal fistula may be identified using flexible bronchoscopy. A high level of suspicion must be maintained, as a bronchoesophageal fistula may not be readily visible depending on the location of the fistula. Techniques using simultaneous esophagoscopy or intubation of the esophagus may need to be performed to confirm the presence of a bronchoesophageal fistula.

Lower Airway Inflammation

Flexible bronchoscopy allows for a visual assessment of the lower airway secretion burden and degree of mucosal inflammation related to chronic pulmonary aspiration, though these are nonspecific findings. The presence of thin and frothy secretions in the lower airways may raise suspicion for salivary aspiration; however, lower airway secretions may appear purulent depending on the degree and duration of the aspiration (Fig. 22.4). In severe cases, food matter may be

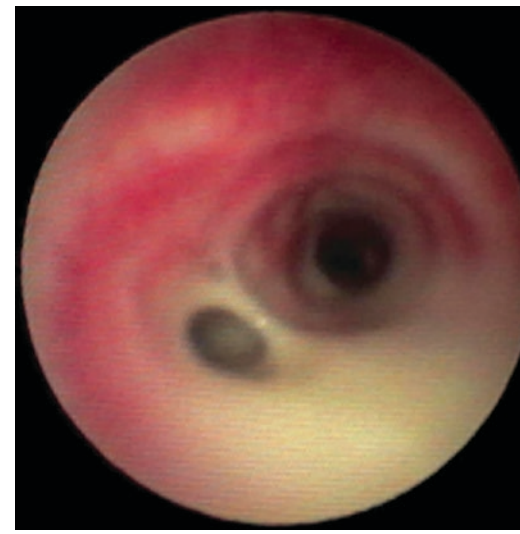

Fig. 22.4 Purulent secretions in the distal trachea and mainstem bronchi in a patient with chronic pulmonary aspiration

visualized in the lower airways. On occasion, gastroesophageal refluxate can be visualized at the level of the larynx, spilling over into the subglottis and lower airways. Children may have extensive mucus plugging of the distal airways, especially in cases where the child has developed bronchiectasis.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) should be performed as part of the initial evaluation of the child with pulmonary aspiration. BAL may be useful to identify organisms causing chronic infection and to quantify the degree of inflammation present in the lower airways. Unfortunately, there is no test that will definitively diagnose a patient with aspiration. Rather, BAL can help lend supportive evidence to the diagnosis.

The presence of upper airway squamous cells on bronchoalveolar lavage may suggest a history of chronic aspiration of upper airway secretions. Caution should be taken in the interpretation of the presence of squamous cells as contamination of the bronchoscope or the lower airways could occur if a trans-nasal approach is used or if aspiration occurs at any point during induction of anesthesia.

The degree of neutrophilic inflammation may be a useful marker for aspiration, though again this is a nonspecific finding. On one study of 100 subjects with chronic aspiration, the average percent neutrophils on BAL was approximately 45% regardless of whether or not there was documented bronchiectasis on chest imaging [5]. While improvement in the degree of inflammation following interventions to address aspiration may provide some reassurance that aspiration has improved, patients with some degree of lung disease or bronchiectasis may continue to have neutrophilic inflammation even after aspiration is addressed.

In theory, lipid present in ingested food or drink or aspirated stomach contents may be present on BAL analysis in the form of lipid-laden macrophages. Studies have shown an increased presence of lipid-laden macrophages in a rabbit model for aspiration [68]. A difference in the lipid-laden macrophage index between children who are known to aspirate and children without aspiration has been noted [69]. Likewise, clinical studies have shown elevated lipid-laden macrophages in children with documented gastroesophageal reflux on pH-probe studies [70]. Conversely, other studies have shown elevated lipid-laden macrophages present in children with lung disease not related to aspiration [71]. Furthermore, elevated lipid-laden macrophages do not necessarily correlate with the degree of inflammation [72]. A review of 100 children with known chronic pulmonary aspiration revealed that 72% of the subjects had less than 5% of macrophages staining for lipid [5]. Unfortunately, lipid-laden macrophages are neither sensitive nor specific for pulmonary aspiration and should not be used as the sole test to diagnose pulmonary aspiration in children.

The presence of pepsin in the lower airways has also been investigated as a potential biomarker for pulmonary aspiration. Pepsin is a proteolytic enzyme made in the stomach, the presence of which in the upper or lower airways could suggest gastroesophageal reflux or aspiration. Early studies revealed increased pepsin levels in tracheal aspirates among children with chronic respiratory symptoms and gastroesophageal reflux [73]. Studies evaluating pepsin obtained from bronchoscopy have not revealed a significant correlation with gastroesophageal reflux [74]. Recent studies have shown that salivary pepsin may not even be a reliable biomarker for extra-esophageal reflux with current methods of measurement [75]. At this time, further testing into the relationship between airway pepsin and lung inflammation with and without a history of pulmonary aspiration is needed.

The Aerodigestive Model

The aerodigestive model allows for a coordinated approach to the evaluation of the child with complex and interrelated symptoms related to breath-

ing and swallowing due to airway disorders and airway obstruction, chronic lung disease, gastroesophageal reflux, eosinophilic esophagitis, esophageal dysmotility, and dysphagia with resultant chronic pulmonary aspiration [76]. The number of aerodigestive centers has been rapidly increasing to care for a growing number of patients with aerodigestive disorders [77, 78]. The interdisciplinary model relies on planned coordination of studies and procedures with multiple specialists to reduce the time to complete a thorough evaluation. This coordination of care has resulted in a decrease in hospital charges due to a reduction in the number of clinic visits and anesthetics needed to complete the evaluation [79]. A key component of the evaluation is the "triple scope" which includes flexible bronchoscopy, rigid bronchoscopy, and esophagogastroduodenoscopy performed under the same anesthetic. Other components of the evaluation as described in this chapter may be scheduled in the days surrounding the "triple scope" to provide efficient scheduling. Team members meet to discuss the patient's symptoms before and after the evaluation and are able to provide the family with a clear and defined plan to address the patient's symptoms and the family's concerns. This coordinated interdisciplinary approach has the potential to improve the ability to diagnose and treat children with chronic pulmonary aspiration while reducing cost and the burden of the evaluation on families.

Conclusion

Pulmonary aspiration is a common problem in pediatrics. Flexible bronchoscopy and bronchoalveolar lavage are useful tools in the diagnosis and management of chronic pulmonary aspiration. The aerodigestive model provides an efficient and cost-effective way to coordinate the various studies and procedures that may be indicated in the evaluation of the child with chronic pulmonary aspiration.

References

1. Boesch RP, Daines C, Willging JP, Kaul A, Cohen AP, Wood RE, Amin RS. Advances in the diagnosis and management of chronic pulmonary aspiration in children. Eur Respir J. 2006;28:847–61.
2. Hu X, Lee JS, Pianosi PT, Ryu JH. Aspiration-related pulmonary syndromes. Chest. 2015;147:815–23.
3. Boesch RP, DeBoer EM. Aspiration. In: Wilmott RW, Deterding R, Li A, Ratjen F, Sly P, Zar H, Bush A, editors. Kendig and Chernick's disorders of the respiratory tract in children. 9th ed. Philadelphia: Elsevier; 2019. p. 1097–105.
4. Barnes TW, Vassallo R, Tazelaar HD, Hartman TE, Ryu JH. Diffuse bronchiolar disease due to chronic occult aspiration. Mayo Clin Proc. 2006;81:172–6.
5. Piccione JC, McPhail GL, Fenchel MC, Brody AS, Boesch RP. Bronchiectasis in chronic pulmonary aspiration: risk factors and clinical implications. Pediatr Pulmonol. 2012;47:447–52.
6. Miller JL, Sonies BC, Macedonia C. Emergence of oropharyngeal, laryngeal and swallowing activity in the developing fetal upper aerodigestive tract: an ultrasound evaluation. Early Hum Dev. 2003;71:61–87.
7. Delaney AL, Arvedson JC. Development of swallowing and feeding: prenatal through first year of life. Dev Disabil Res Rev. 2008;14:105–17.
8. Miller CK, Maybee J, Prager JD, Pentiuk S. Feeding and swallowing disorders. In: Wilmott RW, Deterding R, Li A, Ratjen F, Sly P, Zar H, Bush A, editors. Kendig and Chernick's disorders of the respiratory tract in children. 9th ed. Philadelphia: Elsevier; 2019. p. 1106–13.
9. Sheikh S, Allen E, Shell R, Hruschak J, Iram D, Castile R, McCoy K. Chronic aspiration without gastroesophageal reflux as a cause of chronic respiratory symptoms in neurologically normal infants. Chest. 2001;120:1190–5.
10. Horn SD, Smout RJ. Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes. J Pediatr. 2003;143:S133–41.
11. Kelly MM. The medically complex premature infant in primary care. J Pediatr Health Care. 2006;20:367–73.
12. Friedrich L, Pitrez PM, Stein RT, Goldani M, Tepper R, Jones MH. Growth rate of lung function in healthy preterm infants. Am J Respir Crit Care Med. 2007;176:1269–73.
13. Bae SO, Lee GP, Seo HG, Oh BM, Han TR. Clinical characteristics associated with aspiration or penetration in children with swallowing problem. Ann Rehabil Med. 2014;38:734–41.
14. Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. Pediatr Neurol. 2015;52:143–52.
15. Stensvold HJ, Klingenberg C, Stoen R, Moster D, Braekke K, Guthe HJ, Astrup H, Rettedal S, Gronn

M, Ronnestad AE. Norwegian Neonatal Network Neonatal morbidity and 1-year survival of extremely preterm infants. Pediatrics. 2017;139(3):e20161821.
16. Horbar JD, Edwards EM, Greenberg LT, Morrow KA, Soll RF, Buus-Frank ME, Buzas JS. Variation in performance of neonatal intensive care units in the United States. JAMA Pediatr. 2017;171(3):e164396.
17. Cotton RT, Balakrishnan K. The Aerodigestive model: improving health care value for complex patients through coordinated care. In: Wilmott RW, Deterding R, Li A, Ratjen F, Sly P, Zar H, Bush A, editors. Kendig and Chernick's disorders of the respiratory tract in children. 9th ed. Philadelphia: Elsevier; 2019. p. 1094–6.
18. Boesch RP, Balakrishnan K, Acra S, Benscoter DT, Cofer SA, Collaco JM, Dahl JP, Daines CL, DeAlarcon A, DeBoer EM, Deterding RR, Friedlander JA, Gold BD, Grothe RM, Hart CK, Kazachkov M, Lefton-Greif MA, Miller CK, Moore PE, Pentiuk S, Peterson-Carmichael S, Piccione J, Prager JD, Putnam PE, Rosen R, Rutter MJ, Ryan MJ, Skinner ML, Torres-Silva C, Wootten CT, Zur KB, Cotton RT, Wood RE. Structure and functions of pediatric aerodigestive programs: a consensus statement. Pediatrics. 2018;141(3):e20171701.
19. Gleeson K, Eggli DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. Chest. 1997;111(5):1286–72.
20. Appel JZ, Lee SM, Hartwig MG, Li B, Hsieh CC, Cantu E, Yoon Y, Lin SS, Parker W, Davis RD. Characterization of the innate immune response to chronic aspiration in a novel rodent model. Respir Res. 2007;8:87.
21. Matsuse T, Oka T, Kida K, Fukuchi Y. Importance of diffuse aspiration bronchiolitis caused by chronic occult aspiration in the elderly. Chest. 1996;110:1289–93.
22. Kang EY, Miller RR, Muller NL. Bronchiectasis: comparison of preoperative thin-section CT and pathologic findings in resected specimens. Radiology. 1995;195:649–54.
23. Douros K, Alexopoulou E, Nicopoulou A, Anthracopoulos MB, Fretzayas A, Yiallouros P, Nicolaidou P, Priftis KN. Bronchoscopic and high-resolution CT scan findings in children with chronic wet cough. Chest. 2011;140:317–23.
24. Selley WG, Ellis RE, Flack FC, Brooks WA. Coordination of sucking, swallowing and breathing in the newborn: its relationship to infant feeding and normal development. Br J Disord Commun. 1990;25:311–27.
25. Stevenson RD, Allaire JH. The development of normal feeding and swallowing. Pediatr Clin N Am. 1991;38:1439–53.
26. Ayano R, Tamura F, Ohtsuka Y, Mukai Y. The development of normal feeding and swallowing: Showa University study of the feeding function. Int J Orofacial Myology. 2000;26:24–32.
27. Murray J, Langmore SE, Ginsberg S, Dostie A. The significance of accumulated oropharyngeal secretions and swallowing frequency in predicting aspiration. Dysphagia. 1996;11:99–103.
28. Link DT, Willging JP, Miller CK, Cotton RT, Rudolph CD. Pediatric laryngopharyngeal sensory testing during flexible endoscopic evaluation of swallowing: feasible and correlative. Ann Otol Rhinol Laryngol. 2000;109:899–905.
29. Thompson DM. Laryngopharyngeal sensory testing and assessment of airway protection in pediatric patients. Am J Med. 2003;115(Suppl 3A):166S–8S.
30. Thach BT. Maturation of cough and other reflexes that protect the fetal and neonatal airway. Pulm Pharmacol Ther. 2007;20(4):365–70.
31. Orenstein SR, Orenstein DM. Gastroesophageal reflux and respiratory disease in children. J Pediatr. 1988;112:847–58.
32. Orenstein SR. An overview of reflux-associated disorders in infants: apnea, laryngospasm, and aspiration. Am J Med. 2001;111(Suppl 8A):60S–3S.
33. Berquist WE, Rachelefsky GS, Kadden M, Siegel SC, Katz RM, Fonkalsrud EW, Ament ME. Gastroesophageal reflux-associated recurrent pneumonia and chronic asthma in children. Pediatrics. 1981;68:29–35.
34. Chen PH, Chang MH, Hsu SC. Gastroesophageal reflux in children with chronic recurrent bronchopulmonary infection. J Pediatr Gastroenterol Nutr. 1991;13:16–22.
35. Harding SM. Gastroesophageal reflux and asthma: insight into the association. J Allergy Clin Immunol. 1999;104:251–9.
36. Harding SM. Gastroesophageal reflux, asthma, and mechanisms of interaction. Am J Med. 2001;111(Suppl 8A):8S–12S.
37. Harding SM. Pulmonary manifestations of gastroesophageal reflux. Clin Perspect Gastroenterol. 2002;5:269–73.
38. Rudolph CD. Supraesophageal complications of gastroesophageal reflux in children: challenges in diagnosis and treatment. Am J Med. 2003;115(Suppl 3A):150S–6S.
39. Weinberger M. Gastroesophageal reflux disease is not a significant cause of lung disease in children. Pediatr Pulmonol Suppl. 2004;26:197–200.
40. Eid NS. Gastroesophageal reflux is a major cause of lung disease-pro. Pediatr Pulmonol Suppl. 2004;26:194–6.
41. Donnelly RJ, Berrisford RG, Jack CI, Tran JA, Evans CC. Simultaneous tracheal and esophageal pH monitoring: investigating reflux-associated asthma. Ann Thorac Surg. 1993;56:1029–33; discussion 1034
42. Jack CI, Calverley PM, Donnelly RJ, Tran J, Russell G, Hind CR, Evans CC. Simultaneous tracheal and oesophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. Thorax. 1995;50:201–4.
43. Phua SY, McGarvey LP, Ngu MC, Ing AJ. Patients with gastro-oesophageal reflux disease and cough have impaired laryngopharyngeal mechanosensitivity. Thorax. 2005;60:488–91.

44. Morton RE, Wheatley R, Minford J. Respiratory tract infections due to direct and reflux aspiration in children with severe neurodisability. Dev Med Child Neurol. 1999;41:329–34.
45. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol. 1946;52:191–205.
46. Schwartz DJ, Wynne JW, Gibbs CP, Hood CI, Kuck EJ. The pulmonary consequences of aspiration of gastric contents at pH values greater than 2.5. Am Rev Respir Dis. 1980;121:119–26.
47. Downing TE, Sporn TA, Bollinger RR, Davis RD, Parker W, Lin SS. Pulmonary histopathology in an experimental model of chronic aspiration is independent of acidity. Exp Biol Med (Maywood). 2008;233:1202–12.
48. Raghavendran K, Davidson BA, Mullan BA, Hutson AD, Russo TA, Manderscheid PA, Woytash JA, Holm BA, Notter RH, Knight PR. Acid and particulate-induced aspiration lung injury in mice: importance of MCP-1. Am J Physiol Lung Cell Mol Physiol. 2005;289:L134–43.
49. Kuhn JP, Brody AS. High-resolution CT of pediatric lung disease. Radiol Clin N Am. 2002;40(1):89–110.
50. Long FR, Castile RG, Brody AS, Hogan MJ, Flucke RL, Filbrun DA, McCoy KS. Lungs in infants and young children: improved thin-section CT with a noninvasive controlled-ventilation technique – initial experience. Radiology. 1999;212:588–93.
51. Reid LM. Reductions in bronchial subdivisions in bronchiectasis. Thorax. 1950;5:233–47.
52. Gaillard EA, Carty H, Heaf D, Smyth RL. Reversible bronchial dilatation in children: comparison of serial high-resolution computer tomography scans of the lungs. Eur J Radiol. 2003;47(3):215–20.
53. Miller CK. Clinical oral motor feeding assessment. In: Willging JP, Miller CK, Cohen AP, editors. Pediatric dysphagia: etiologies, diagnosis, and management. 1st ed. San Diego: Plural Publishing; 2020. p. 289–325.
54. DeMatteo C, Matovich D, Hjartarson A. Comparison of clinical and videofluoroscopic evaluation of children with feeding and swallowing difficulties. Dev Med Child Neurol. 2005;47(3):149–57.
55. Langmore SE, Schatz K, Olsen N. Fiberoptic endoscopic examination of swallowing safety: a new procedure. Dysphagia. 1988;2(4):216–9.
56. Miller CK, Willging JP, Strife JL, Rudolph CD. Fiberoptic endoscopic examination of swallowing in infants and children with feeding disorders. Dysphagia. 1994;9:266.
57. Miller CK, Willging JP. Fiberoptic endoscopic evaluation of swallowing in infants and children: protocol, safety, and clinical efficacy: 25 years of experience. Ann Otol Rhinol Laryngol. 2019;17:3489419893720.
58. Cameron J, Reynolds J, Zuidema G. Aspiration in patients with tracheostomies. Surg Gynecol Obstet. 1973;136(1):68–70.
59. Béchet S, Hill F, Gilheaney O, Walshe M. Diagnostic accuracy of the modified Evan's blue dye test in patients with tracheostomy: a systematic review of the evidence. Dysphagia. 2016;31(6):721–9.
60. Rosen R, Amirault J, Johnston N, Haver K, Khatwa U, Rubinstein E, Nurko S. The utility of endoscopy and multichannel intraluminal impedance testing in children with cough and wheezing. Pediatr Pulmonol. 2014;49(11):1090–6.
61. Adil E, Al Shemari H, Kacprowicz A, Perez J, Larson K, Hernandez K, Kawai K, Cowenhoven J, Urion D, Rahbar R. Evaluation and management of chronic aspiration in children with normal upper airway anatomy. JAMA Otolaryngol Head Neck Surg. 2015;141(11):1006–11.
62. Kalinowski CP, Kirsch JR. Strategies for prophylaxis and treatment for aspiration. Best Pract Res Clin Anaesthesiol. 2004;18(4):719–37.
63. Adil E, Gergin O, Kawai K, Rahbar R, Watters K. Usefulness of upper airway endoscopy in the evaluation of pediatric pulmonary aspiration. JAMA Otolaryngol Head Neck Surg. 2016;142(4):339–43.
64. Rosen R, Mitchell PD, Amirault J, Amin M, Watters K, Rahbar R. The edematous and erythematous airway does not denote pathologic gastroesophageal reflux. J Pediatr. 2017;183:127–31.
65. Boesch RP, Baughn JM, Cofer SA, Balakrishnan K. Trans-nasal flexible bronchoscopy in wheezing children: diagnostic yield, impact on therapy, and prevalence of laryngeal cleft. Pediatr Pulmonol. 2018;53(3):310–5.
66. Masters IB, Chang AB, Patterson L, Wainwright C, Buntain H, Dean BW, Francis PW. Series of laryngomalacia, tracheomalacia, and bronchomalacia disorders and their associations with other conditions in children. Pediatr Pulmonol. 2002;34(3):189–95.
67. Lal DR, Oldham KT. Recurrent tracheoesophageal fistula. Eur J Pediatr Surg. 2013;23(3):214–8.
68. Colombo JL, Hallberg KT, Sammut PH. Time course of lipid-laden pulmonary macrophages with acute and recurrent mild aspiration in rabbits. Pediatr Pulmonol. 1992;12(2):95–8.
69. Colombo JL, Hallberg TK. Recurrent aspiration in children: lipid-laden alveolar macrophage quantitation. Pediatr Pulmonol. 1987;3(2):86–9.
70. Sacco O, Fregonese B, Silvestri M, Sabatini F, Mattioli G, Rossi GA. Bronchoalveolar lavage and esophageal pH monitoring data in children with "difficult to treat" respiratory symptoms. Pediatr Pulmonol. 2000;30(4):313–9.
71. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. Pediatr Pulmonol. 1999;27(6):419–22.
72. Kazachkov MY, Muhlebach MS, Livasy CA, Noah TL. Lipid-laden macrophage index and inflammation in bronchoalveolar lavage fluids in children. Eur Respir J. 2001;18(5):790–5.
73. Krishnan U, Mitchell JD, Messina I, Day AS, Bohane TD. Assay of tracheal pepsin as a marker of reflux aspiration. J Pediatr Gastroenterol Nutr. 2002;35(3):303–8.

74. Rosen R, Johnston N, Hart K, Khatwa U, Nurko S. The presence of pepsin in the lung and its relationship to pathologic gastroesophageal reflux. Neurogastroenterol Motil. 2012;24(2):129–33.
75. Dy F, Amirault J, Mitchell PD, Rosen R. Salivary pepsin lacks sensitivity as a diagnostic tool to evaluate extraesophageal reflux disease. J Pediatr. 2016;177:53–8.
76. Piccione J, Boesch RP. The multidisciplinary approach to pediatric aerodigestive disorders. Curr Probl Pediatr Adolesc Health Care. 2018;48(3):66–70.
77. Gumer L, Rosen R, Gold BD, Chiou EH, Greifer M, Cohen S, Friedlander JA. Size and prevalence of pediatric aerodigestive programs in 2017. J Pediatr Gastroenterol Nutr. 2019;68(5):e72–6.
78. Wootten CT, Belcher R, Francom CR, Prager JD. Aerodigestive programs enhance outcomes in pediatric patients. Otolaryngol Clin N Am. 2019;52(5):937–48.
79. Collaco M, Aherrera AD, Au Yeung KJ, Lefton-Greif MA, Hoch J, Skinner ML. Interdisciplinary pediatric aerodigestive care and reduction in health care costs and burden. JAMA Otolaryngol Head Neck Surg. 2015;141(2):101–5.

Plastic Bronchitis

23

Michael D. Davis and Bruce K. Rubin

Overview of Plastic Bronchitis

Plastic bronchitis is a rare disease, first described by Galen, in which branching casts are formed in the airways [1–3]. These casts physically obstruct the airways and cause respiratory distress that can lead to fatal respiratory failure. Patients typically present with symptoms of a lower respiratory tract infection which can include dyspnea, shortness of breath, cough, chest pain, and wheezing [1–3]. One physical finding that is said to be characteristic of plastic bronchitis is the "*bruit de drapeau,*" which translates to the sound of a flag snapping [4]. Although this is an uncommon finding even in patients with known airway casts, it indicates a cast that is "flapping" during inspiration and exhalation and this can sometimes be sensed by patients.

The diagnosis of plastic bronchitis is made by direct observation of casts that are expectorated or visualized during bronchoscopic removal in association with known underlying disease including congenital heart disease with single ventricle physiology, sickle cell acute chest syndrome, hypersecretory eosinophilic bronchitis, and local or systemic lymphatic abnormalities (Table 23.1). Of note, plastic bronchitis has never been reliably described in patients with cystic fibrosis or with non-CF bronchiectasis and the sputum plugs that characterize these diseases are physically and morphologically distinct from the branching casts that define plastic bronchitis. Treatment options historically focused on facilitating cast removal; however, treatments have recently been developed that can prevent cast formation.

Table 23.1 Conditions associated with plastic bronchitis

Proven conditions
Congenital heart diease with Fontan physiology
Pulmonary lymphatic anomalies
Influenza A H1N1 infection
Possible conditions
Toxic inhalation
Sickle cell acute chest syndrome
Hypersecretory and near-fatal asthma (eosinophilic casts)
Unlikely and unproven conditions
Cystic fibrosis
Chronic obstructive pulmonary disease
Bronchiectasis
Bacterial pneumonia

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_23

Causes of Plastic Bronchitis

Although the exact mechanism of cast formation has not been established, contributing factors have been identified and several classification systems of plastic bronchitis types have been proposed. Most patients with plastic bronchitis present after surgical correction of congenital cardiac abnormalities, and it has previously been proposed to categorize plastic bronchitis as cardiac and non-cardiac [5]. Inflammatory and non-inflammatory types of plastic bronchitis, based on histopathological findings within casts, have also been proposed [2, 6]. However, inflammation is a feature of all plastic bronchitis exacerbations. Although cast formation is usually not decreased with the use of anti-inflammatory medications like corticosteroids, exceptions to this are discussed later. Recent advancements in lymphatic imaging and lymphangiography indicate that there are two predominant types of plastic bronchitis: plastic bronchitis with abnormal pulmonary lymphatic circulation including most, if not all, of the patients with congenital heart disease, and plastic bronchitis associated with airway eosinophilia and breakdown products of eosinophils including Charcot-Leyden crystals [1, 7, 8].

Diagnosis of Plastic Bronchitis

Although the diagnosis is based on the presence of branching casts, more specific diagnostic testing to indicate the cause/type of plastic bronchitis should be done. Dynamic contrast magnetic resonance lymphangiography (DCMRL) allows for the imaging of the thoracic duct and will indicate abnormal lymphatic vessels and flow in the lungs [7]. In short, DCMRL involves an MRI of the thoracoabdominal region of patients after injection of contrast dyes into the lymph nodes of the groin. This contrast flows through the thoracic duct and will allow for visualizing of abnormal lymphatic circulation. This can help guide treatments, as discussed below. Histopathologic examination of casts can also be of benefit for indicating the presence of eosinophilic and neutrophilic inflammatory mediators and those patients with eosinophilic bronchitis and cast formation, with or without asthma, may derive some benefit from corticosteroid therapy.

Therapy for Plastic Bronchitis

Medical Management

For stable patients with plastic bronchitis that are capable of expectorating casts, initial therapies are often aimed to "loosen" casts and facilitate expectoration (Table 23.2). Once casts are removed, the focus of care changes to the preven-

Table 23.2 Recommendations for therapy

Good evidence
Selective embolization or gluing of aberrant lymphatic
Thoratic duct ligation
Airway clearance, including physical therapy devices like high-frequency chest compression vest
Aerosolized heparin
Cardiac transplant
Improving cardiac function
Anecdotal or case report evidence
Hyperosmolar saline
Low-dose oral macrolides (clarithromycin or azithromycin)
Oral or inhald corticosteroids (only for eosinophilic casts)
Aerosol tissue plasminogen activator
No evidence and potentially harmful
Beta agonist aerosol
Dornase alfa (Pulmozyme)
Mucolytics such as *N*-acetylcysteine
Expectorants such as guaifenesin
Nonmacrolide antibiotics
Modifications of Fontan (fenestration or fake-down)

Image 23.1 Plastic bronchitis casts. Left, a spontaneously expectorated cast from a patient with known congenital heart disease and suspected abnormal pulmonary lymphatic circulation; right, a cast bronchoscopically cryoextracted from the left lower lobe of a patient with normal pulmonary lymphatic circulation and airway eosinophilia

tion of cast formation. For lymphatic plastic bronchitis, the most effective preventative treatments are interventional. The most effective medical treatments for the prevention of cast production in non-lymphatic plastic bronchitis are mechanical airway clearance therapies, inhaled heparin, and systemic corticosteroid therapy. Evidence supports the use of inhaled aerosolized tissue plasminogen activator (tPA); however, this can cause airway irritation and hemoptysis, especially with prolonged use. Inhaled heparin has been reported to decrease cast formation and has anti-inflammatory properties; therefore, a trial of inhaled heparin is preferred before starting aerosolized tPA [1, 2].

Some anecdotal and case report evidence have claimed benefits from hyperosmolar saline, oral macrolides, and inhaled corticosteroids. No benefit has been demonstrated from the use of inhaled beta-agonists, dornase alfa, or N-acetylcysteine. Since non-lymphatic plastic bronchitis is often associated with eosinophilic histopathologic findings, the use of anti-IL-5 medications, which are now commercially available, may be of benefit. However, the supportive evidence for this potential therapy is lacking [1].

Interventional Management

Bronchoscopy

For patients in acute distress or unable to expectorate casts, rigid or flexible bronchoscopic removal may be required. Casts should be kept as intact as possible during removal to prevent airway obstruction from pieces moving distally. This can be difficult due to the size of casts, which may exceed the size of artificial airways or bronchoscopic channels; or due to the consistency of casts, which is often friable.

Plastic bronchitis casts frequently fill the lumen of pulmonary segments and can therefore be several centimeters in size (Image 23.1). The size of airway casts often precludes removal through the lumen of even a rigid bronchoscope. In this way, removal of casts resembles removal of large, slippery, friable foreign bodies from the airways. When removing a cast from the airways, care must be taken to prevent tracheal obstruction while maintaining airway control. If a cast becomes stuck in the trachea or artificial airway of the patient, ventilation may become impossible; therefore, it is often appropriate to remove the cast along with the

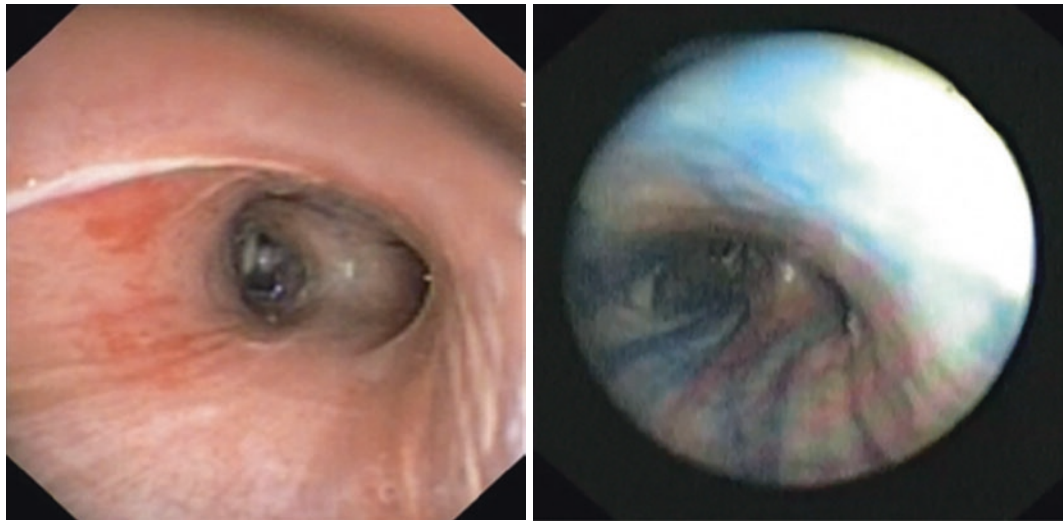

Image 23.2 Bronchoscopic visual confirmation of abnormal pulmonary lymphatic flow. These airway images are taken from a bronchoscope after plastic bronchitis cast removal. During percutaneous lymphatic catheterization, blue dye is injected into the lymphatic vessels suspected of flowing toward affected bronchi. Photos are taken pre- (left) and post-injection (right) of blue dye and the blue dye is easily visualized after injection, indicating the suspected lymphatic vessels do flow to the areas in which casting occurs

bronchoscope and artificial airway rather than pull the cast through the bronchoscope port or airway. Removal of the artificial airway (endotracheal tube, laryngeal mask airway, or rigid bronchoscope) may be a significant risk for patients that are ventilator dependent, acutely ill, or have a difficult airway. Also, repeated removal and reinsertion of the bronchoscope or artificial airway increase the risk of laryngotracheal trauma. An appropriate support team for bronchoscopy, airway management, and resuscitation should be available during the removal of large airway casts.

The consistency of casts also makes their removal challenging. Plastic bronchitis casts are often described as being similar to toothpaste or putty – firm enough to occlude a suction port, yet too slippery and friable to be removed intact with forceps [2]. Most case reports have used a combination of forceps and suction to remove casts. This approach typically leads to the casts being broken and removed in pieces with the most distal pieces of the cast beyond the vision of the bronchoscope left behind. Cryoextraction, using a flexible cryoprobe that can be introduced through rigid or flexible bronchoscopes, may facilitate the removal of more intact casts [9]. This technique involves penetration of a cryoprobe into the proximal end of a cast. The cast is then frozen from the middle outward and removed along with the cryoprobe and bronchoscope. Care must be taken to prevent cold-induced trauma to the airway walls surrounding casts; once the cast is visibly frozen, it should be rapidly removed.

Percutaneous Pulmonary Lymphatic Embolization

Patients diagnosed with plastic bronchitis with aberrant lymphatic flow confirmed by DCMRL will benefit from percutaneous pulmonary lymphatic embolization. Some reports have shown complete resolution of plastic bronchitis symptoms in patients with aberrant lymphatic flow post-embolization [7, 8]. This procedure involves fluoroscopy-guided

percutaneous catheterization of the thoracic duct and glue embolization of the abnormal pulmonary lymphatic vessels. Further confirmation of the flow of the vessels to affected bronchi can be accomplished by the introduction of dye to the targeted lymphatic vessels with concurrent bronchoscopic observation of the airways; visualization of dye in the airway walls confirms a direct flow connection (Image 23.2).

Conclusion

Plastic bronchitis provides unique challenges to the pediatric bronchoscopist, mostly related to the size and consistency of the airway casts. Cryoextraction facilitates the removal of these casts intact; however, caution must be taken to prevent airway trauma and obstruction. Awareness of the causes and symptoms of plastic bronchitis can alert the clinician to assemble an appropriate support team for difficult cast removal.

References

1. Rubin BK. Plastic bronchitis. Clin Chest Med. 2016;37:405–8.
2. Madsen P, Shah SA, Rubin BK. Plastic bronchitis: new insights and a classification scheme. Paediatr Respir Rev. 2005;6:292–300.
3. Johnson RS, Sit-Lumsden EG. Plastic bronchitis. Thorax. 1960;15:325–32.
4. Werkhaven J, Holinger LD. Bronchial casts in children. Ann Otol Rhinol Laryngol. 1987;96:86–92.
5. Seear M, Hui H, Magee F, Bohn D, Cutz E. Bronchial casts in children: a proposed classification based on nine cases and a review of the literature. Am J Respir Crit Care Med. 1987;155:364–70.
6. Brogan TV, Finn LS, Pyskaty DJ, et al. Plastic bronchitis in children: a case series and review of the medical literature. Pediatr Pulmonol. 2002;34:482–7.
7. Dori Y. Novel lymphatic imaging techniques. Tech Vasc Interv Radiol. 2016;19:255–61.
8. Itkin M. Interventional treatment of pulmonary lymphatic anomalies. Tech Vasc Interv Radiol. 2016;19:299–304.
9. DiBardino DM, Lanfranco AR, Haas AR. Bronchoscopic cryotherapy: clinical applications of the cryoprobe, cryospray, and cryoadhesion. Ann Am Thorac Soc. 2016;13:1405–15.

Flexible Bronchoscopy and Pediatric Asthma

24

Mikhail Kazachkov

Introduction

Asthma is the most common chronic disease of childhood with close to 7% of children reported to be affected in the United States [1] and is one of the best-studied pediatric diseases with more than 45,000 PubMed citations.

Until recently, pediatric asthma has not been considered a common indication for bronchoscopy. One of the larger reviews of pediatric bronchoscopy analyzed 57,145 procedures performed between 2012 and 2014 by 198 centers from 33 European countries, and "asthma" was not included in the list of 25 most common indications for bronchoscopy in children [2]. Similarly, pediatric asthma guidelines [3], despite providing an excellent overview of the diagnosis and management of asthma, do not even mention the role of flexible bronchoscopy and related procedures in pediatric asthma. This chapter describes the implication of flexible bronchoscopy, bronchoalveolar lavage (BAL), and endobronchial biopsy (EBB) in the diagnosis and differential diagnosis of pediatric asthma with special attention to their role in establishing specific asthma phenotypes and creating individualized management plans for children with severe uncontrolled asthma.

Safety of Flexible Bronchoscopy in Asthma

The most comprehensive safety data on flexible bronchoscopy in adult asthma come from the Severe Asthma Research Program [4]. Flexible bronchoscopy was performed on 436 asthmatic patients, 143 of whom had severe and very severe asthma. Only five of the subjects had asthma exacerbations after bronchoscopy. Minimal worsening of pulmonary function was noticed immediately after the procedure; it was not different in subjects with severe versus mild asthma. Of note, all study subjects obtained albuterol nebulization prior to bronchoscopy as part of the pulmonary function testing protocol. BAL and EBB were obtained respectively on 92% and 98% of subjects with severe, and 78% and 95% of subjects with very severe asthma, but their impact could not be analyzed separately due to the extremely low number of complications. These data, although it cannot be readily applied to pediatric patients, are reassuring on the safety of bronchoscopy and BAL in asthmatic children who tend to have in general much better lung function than adults with severe asthma.

Electronic Supplementary Material: The online version of this chapter (https://doi.org/10.1007/978-3-030-54924-4_24) contains supplementary material, which is available to authorized users.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_24

Safety of flexible bronchoscopy with BAL in pediatrics was assessed by Payne et al. [5] in 38 children with difficult to control asthma. They reported excellent tolerance and an extremely low rate of both procedural complications (oxygen desaturations without bradycardia in one patient) and postprocedural events (increase of symptoms, which required bronchodilator in four patients). Of note, all study patients received a 2-week course of oral prednisolone prior to the procedure for assessment of steroid resistance according to the study protocol.

It has to be said that the use of bronchodilators or/and systemic steroids prior to performing bronchoscopy in pediatric asthma patients has never been validated or shown to improve the safety of the procedure; thus, the decision to use those agents has to be made on an individual basis.

Flexible Bronchoscopy in the Differential Diagnosis of Asthma

Expiratory Wheezing as Indication for Flexible Bronchoscopy

Pulmonary practitioners are very familiar with the famous saying of Professor Chevalier Jackson, "all is not asthma that wheezes," which he expressed in his iconic book, "Bronchoscopy, Esophagoscopy and Gastroscopy" in 1934 [6]. Apparently, this catchy phrase remains of high importance, which can be easily proven by ongoing difficulties related to the differential diagnosis of asthma and other causes of wheezing in children [7, 8]. In the larger study by Gu et al. [9], retrospective analysis of 156 children, who underwent flexible bronchoscopy for persistent wheezing, showed an incidence of airway malformations of 21.8% in older children, and of 31% in infants under 12 months of age.

The format of this chapter does not allow for an in-depth discussion of the differential diagnosis of wheezing; however, certain remarks related to the role of flexible bronchoscopy still have to be made.

There are multiple conditions, which could be easily confused with asthma. They include tracheomalacia (with or without bronchomalacia), tracheal and bronchial compression and stenosis, endotracheal and endobronchial lesions, and foreign bodies of the intrathoracic trachea and bronchi. All of the above are associated with intrathoracic airway obstruction, which changes the physiology of breathing by increasing the intramural pressure vector directed against airway walls causing further narrowing of the airway lumen, which then results in prolonged expiration and wheezing [10] (Fig. 24.1). In most

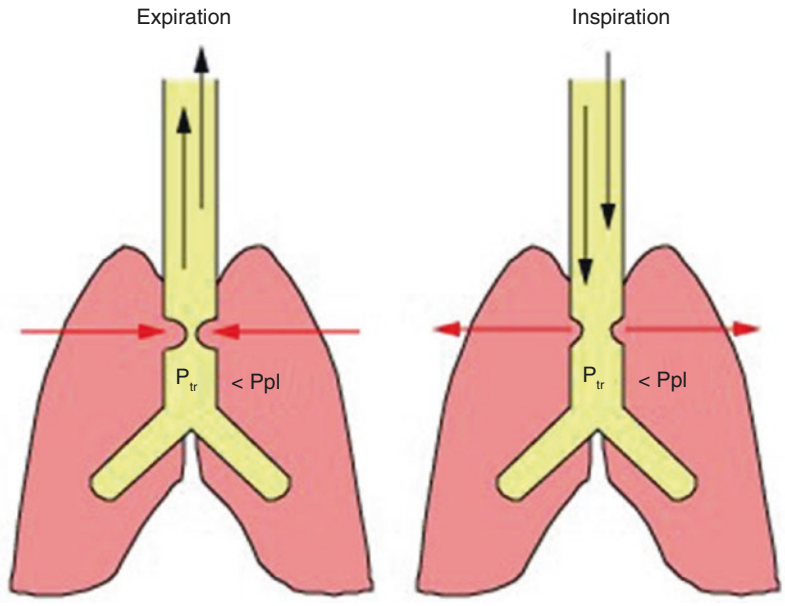

Fig. 24.1 Intrathoracic airway obstruction. Redrawn from Kryger et al. [10]

cases, the presence of intrathoracic airway obstruction unrelated to asthma could be suspected clinically; however, it requires careful history and physical examination with special attention to the following:

Bronchodilator Response

Absence of improvement in wheezing and spirometric features of lower airway obstruction after administration of bronchodilator does not rule out asthma; however, it opens the possibility of an alternative diagnosis [11].

Air Trapping in the Lungs

Presence of bilateral air trapping in the lungs usually points to peripheral airway obstruction, which is typical for uncontrolled asthma [12]. Air trapping may be detected by expiratory volumetric computer tomography in children with tracheomalacia too, but it is most likely explained by peripheral airway disease, caused by chronic bacterial inflammation and small airway malacia [13]. Bilateral air trapping is much less likely to occur in cases of large airway vascular compression or foreign body aspiration. Air trapping could be assessed via chest inspection, which may show "barrel chest" in severe cases but can also be picked up during percussion of the lung, which yields hyperresonant or tympanic sound over the lung fields. Reduced or absent cardiac dullness during percussion of the heart in children with air trapping related to peripheral airway disease was described by Max Klein [14]. Similar sign of air trapping with "loss" of heart dullness was reported in children with viral bronchiolitis [15], another common cause of wheezing related to peripheral airway obstruction. Unfortunately, percussion has become a "forgotten skill" and has been rarely mastered by contemporary practitioners.

Figure 24.2 provides an easy algorithm for topical diagnosis of persistent wheezing based on bronchodilator response and presence of air trapping in the lungs.

Recurrent and Persistent Wheezing in Infants, American Thoracic Society (ATS) Guidelines

In 2016, a group of ATS experts performed a comprehensive review of 10 case series articles [16] that collectively included 1364 patients and

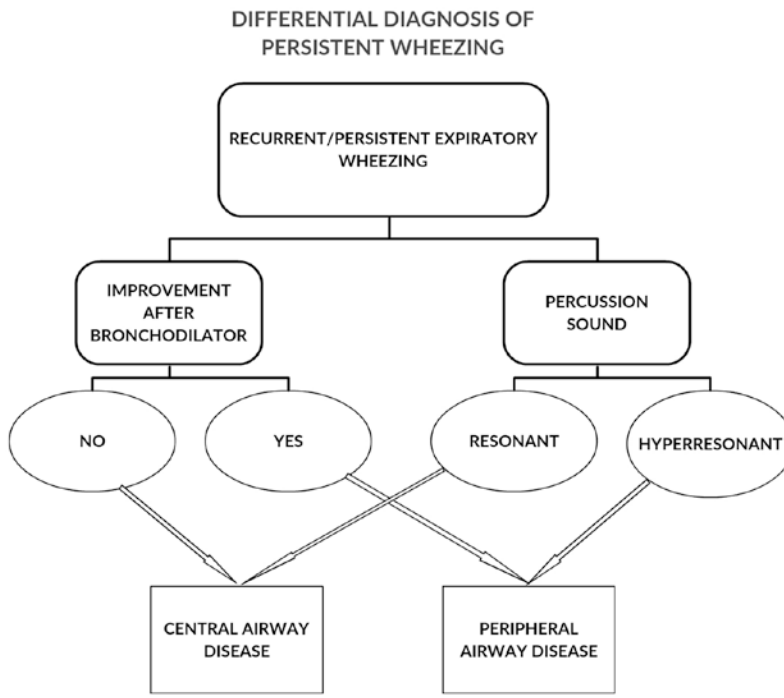

Fig. 24.2 Differential diagnosis of persistent wheezing (Original figure by M. Kazachkov)

reported that 452 of the 1364 patients (33%) who underwent airway survey for respiratory symptoms were found to have an anatomic abnormality known to cause wheezing. The expert committee acknowledged that performance of flexible bronchoscopy in this group of patients presents certain benefits including "relief from the burden, cost, and potential harms of further diagnostic testing; probable reductions in the use of ineffective medications (bronchodilators or systemic corticosteroids) and the frequency of physician visits; and parental reassurance, given the high likelihood that the condition will spontaneously resolve." This review led to the following recommendation: "For infants with persistent wheezing despite treatment with bronchodilators, inhaled corticosteroids, or systemic corticosteroids, we suggest airway survey via flexible fiberoptic bronchoscopy." The group specified that the recommendation for airway survey is conditional and called for a careful selective approach to indication for the procedure and consideration of potential neurodevelopmental risks of anesthesia as well as parental preferences regarding invasive procedures. However, it came as an important step toward the legitimization of flexible bronchoscopy in wheezing infants and reassured pediatric pulmonologists that their approach to persistent wheezing in infancy with flexible bronchoscopy has been valid.

Association of Asthma with Anatomical Airway Abnormalities

Considering the very high prevalence of asthma in the pediatric population, its presence in children with congenital airway abnormalities is a matter of statistical frequency of independent events. On the other hand, it is possible that the presence of certain congenital airway abnormalities may promote aspiration into the airway, impairment of lower airway secretion clearance, development of chronic bacterial airway infection, and thus contribute to airway inflammation and hyperreactivity in children with asthma. In the study of bronchoscopy in wheezing children, Boesch et al. [17] found that one-third of 30 patients with severe asthma enrolled in the study had an anatomical contributor to their wheezing and implication of bronchoscopy led to significant intervention changes in this category of patients.

Tracheo-broncho-malacia (TBM) and excessive dynamic airway collapse (EDAC) are relatively infrequent but well-recognized complications of severe uncontrolled asthma and COPD in older children and adults [18, 19]. Of note, most practitioners separate EDAC from TBM and define it as "pathological collapse and narrowing of the airway lumen by >50%, which is entirely due to the laxity of the posterior wall membrane with structurally intact airway cartilage" [20]. The likely causes of TBM and EDAC in asthma are irritation with cough and cigarette smoke as well as chronic infection, all of which cause the "weakening" of the tracheal structures [21]. Both TBM and EDAC may strongly contribute to the severity of asthma by causing wheezing, exercise-related dyspnea, and impairment of lower respiratory secretion clearance [22]. Despite advances in modern radiological techniques, flexible bronchoscopy remains the "gold standard" for assessing TBM and EDAC in children with asthma, providing excellent visualization and quantitation of dynamic airway collapse [23]. Proper assessment and acknowledgment of the presence of TBM and EDAC often lead to management modifications in children with asthma. Therapeutic modalities include pharmacological treatments aimed toward decreasing the collapsibility of tracheal smooth muscle [24], application of positive airway pressure [25], surgical interventions such as aortopexy [26] and posterior tracheopexy [27], and even placement of tracheal and bronchial stents in older patients [28].

Apparently, coexistence of asthma with congenital or acquired airway abnormalities possesses a diagnostic and management problem due to the overlap of symptoms and potential implications on treatment. This only emphasizes the importance of flexible bronchoscopy, which in this situation serves not only as an excellent

diagnostic tool but also provides the accessibility to the lower airway for additional assessment of severity and type of asthmatic inflammation.

Flexible Bronchoscopy in Severe Uncontrolled Asthma

Pediatric asthma guidelines [3] provide an excellent practical manual on the management of asthma in children. Following the guidelines is important for asthma practitioners, because it makes management of pediatric asthma successful in a vast majority of cases. However, there are certain pediatric patients, which would not improve sufficiently despite all the practitioners' efforts. It has to be stated that nonadherence to asthma treatment regimens has remained the major cause of poor asthma control and has to be carefully addressed prior to assigning the patient into the category of SUA. Hedlin et al. [29] suggested dividing problematic severe asthma into two categories, difficult-to-treat asthma and severe therapy-resistant asthma, after taking into consideration medication adherence (Fig. 24.3). There are multiple names, which have been suggested to define problematic asthma, and they, in addition to those mentioned above, include "severe uncontrolled asthma," "difficult-to-control asthma," "treatment-resistant asthma," "refractory asthma," as well as many others. The fact that existing asthma guidelines have very little to say about the management of this type of asthma [30] prompted the development of ERS/ATS taskforce, which came up with guidelines on the definition, evaluation, and treatment of severe asthma in 2014 [31]. According to it, severe uncontrolled asthma (SUA), the name for the discussed condition we would like to adapt for this chapter, has to be diagnosed "when a diagnosis of asthma is confirmed and comorbidities have been addressed" and is defined as "asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains uncontrolled despite this therapy." True incidence of SUA in pediatrics is difficult to estimate but in accordance with Scandinavian Birth Cohort studies it could occur in 2%–5% of all children with asthma [32]. Considering the very high prevalence of asthma in the pediatric population, many children with SUA suffer from poorly controlled symptoms, frequent exacerbations, and in many cases show rapidly declining lung function, which possesses a major health-care problem and burden [33].

Eosinophilic Airway Inflammation

Presence and severity eosinophilic airway inflammation were shown to be a major characteristic of SUA in children [34, 35]. Noninvasive methods of assessing airway eosinophilia have been implemented into asthma practice and include periph-

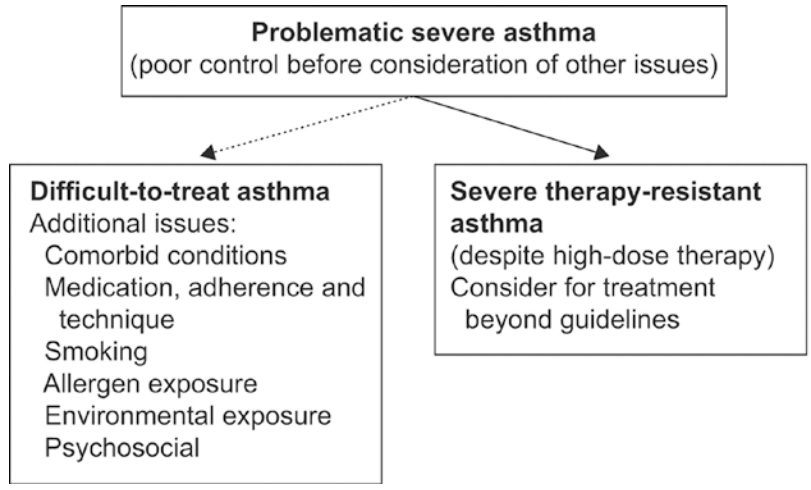

Fig. 24.3 Problematic severe asthma can be divided up into difficult-to-treat asthma and severe therapy-resistant asthma. From Hedlin et al. [29]

eral eosinophilic count, sputum eosinophilia as well as fractional exhaled nitric oxide concentration (FeNO) and some others. Those noninvasive tests, although they allow for relatively easy detection of eosinophilic inflammation, have been proven to be rather inaccurate when compared with more precise techniques. Lex et al. [36] investigated the relationships between FeNO and eosinophils in induced sputum, BAL, and the bronchial subepithelium in a group of 27 children and adolescents with SUA. The concordance between any noninvasive marker and any invasive marker was low and ranged between 59% and 75%. Both sputum eosinophils and FeNO failed to correlate with biopsy eosinophils. These data are in agreement with more recent systematic review and meta-analysis of the value of minimally invasive markers for detection of airway eosinophilia in asthma in children and adults [37], which, after analyzing 32 studies (24 in adults and 8 in children), concluded that even at the optimal cut point, sensitivities and specificities of noninvasive markers for detecting even sputum eosinophilia are moderate, and their use would lead to many false positives or false negatives. All of the above emphasizes the importance of bronchoscopic methods for the assessment of the presence and quantity of eosinophilic lower airway inflammation.

BAL Eosinophils

To begin with, there have been some difficulties with establishing the norms for eosinophilic counts in BAL due to a relative paucity of data on BAL cellularity in children without respiratory symptoms. The founder study by Ratjen et al. [38] showed that children without pulmonary diseases have very few eosinophils in their BAL ($0.4 \pm 0.6\%$). Similarly, low values for BAL eosinophils were found in nonasthmatic children with chronic cough (median 0.1%, 0–1.5% range for 0–95 percentile) [39]. This prompted most practicing bronchologists to interpret ≥1.5% of BAL eosinophils as "elevated." It is known from "classic" adult literature that elevated BAL eosinophils are not specific for any particular pulmonary disease but rather may occur in multiple conditions such as asthma, interstitial lung diseases, acquired immunodeficiency syndrome (AIDS)-associated pneumonia, idiopathic eosinophilic pneumonia, and drug-induced lung disease [40].

The data on BAL eosinophils in SUA in children are limited. Snijers et al. [41] showed that children with asthma have higher BAL eosinophil counts in comparison to children with no asthma, but the children with SUA were not analyzed separately. O'Brien et al. [42] showed a relatively high prevalence of BAL eosinophilia in their group of 32 children with SUA. It was also shown that children with SUA have significantly increased BAL fluid eosinophil counts compared with those seen in control subjects (median, 2.7% [1% to 7.7%] vs 0% [0% to 0.9%], respectively; $P < 0.001$) but the study had no comparison group with milder asthma phenotypes [43]. Finally, the analysis of 350 patients from Severe Asthma Molecular Phenotype cohort showed that children classified as "eosinophilic steroid-refractory phenotype" had significantly more BAL eosinophils than children classified as "recurrent wheeze" [44]. Overall, despite the notion that children with asthma have higher BAL eosinophils counts than children without pulmonary disease, review of existing data makes it difficult to state that there is a correlation between the amount of BAL eosinophils and severity of asthma phenotype.

EBB Eosinophils[1]

The normative data on EBB eosinophils are even scarcer than on BAL; however, it can be suggested that children (as well as adults) without pulmonary disease have very little, if any, eosinophils in their bronchial submucosa [45, 46]. There are several studies, which address airway wall eosinophils in pediatric SUA. Bossley et al. [43] showed that children with SUA have a significantly higher amount of eosinophils in their EBB specimens compared with children without asthma (12.9 (3.3–35.3) cells/mm^3 in atopic subjects with SUA and 4.13 (0–10.98) in nonatopic vs. 0 (0–17.9) and 0 (0) in atopic and nonatopic controls). In another study of 24 pediatric patients with SUA, 67% of them had EBB eosinophils. Importantly, there was only a weak correlation

[1]For more advanced discussion on EBB, please see corresponding chapter of this book.

between BAL and EBB eosinophils with 29% of patients having EBB eosinophils without BAL eosinophils, which emphasized the insufficiency of BAL investigation alone in the assessment of airway eosinophils [47].

Neutrophilic Airway Inflammation

Neutrophilic airway inflammation has been associated with severe adult asthma [48]. However, the frequency and even the existence of neutrophilic asthma in pediatrics have not been convincingly reported [49]. Nevertheless, neutrophilic infiltration of bronchial submucosa was shown to be present in a small subset of pediatric patients with SUA [47]. It was also reported that certain patients with SUA may have intraepithelial rather than submucosal neutrophils. Contrary to the predictions derived from adult literature, this intraepithelial neutrophilic infiltration seemed to be "protective" for children with SUA and was associated with better asthma control and lung function [50]. In addition, BAL neutrophilia in patients with SUA has to be interpreted with caution and frequently can be explained by the microbial overload of the airway of patients with asthma, which will be discussed in more detail later in this chapter.

Assessment of Airway Remodeling

Airway remodeling in asthma is described as structural changes, such as thickening of reticular basement membrane (RBM), airway smooth muscle hypertrophy, and angiogenesis [51]. RBM can be assessed reliably during EBB and is considered the best-studied marker of airway remodeling. There is a proposed relationship between poor asthma control characterized by excess airway inflammation and airway remodeling with the latter resulting in rapid deterioration of lung function in adult patients [52]. However, a systematic review of 39 studies addressing airway remodeling in pediatric asthma by Castro-Rodriguez et al. [53] failed to confirm the primary role of airway inflammation in the development of airway remodeling in children suggesting a more complex relationship between those two entities.

Airway remodeling may occur very early in the course of asthma. Pohunek et al. [54] performed EBB in 27 children with nonspecific respiratory symptoms, 10 of whom later developed full clinical asthma and showed that RBM was greater (4.65 vs. 3.72 microm, $p = 0.044$) in children with bronchial asthma diagnosed at follow-up, compared with the children who did not progress to asthma. These data are in agreement with the findings of another study, which showed a positive correlation of RBM thickness with the frequency and severity of wheezing in infants and small children [55].

Airway remodeling is considered to be an important marker of SUA. It was shown that children with SUA have increased RBM thickness compared with control subjects (7.12 μm [6.37–7.89 μm] vs 4.89 μm [4.16–6.16 μm]; $P < 0.0001$) [43]. In addition, van Mastrigt et al. [56], in a larger study of EBB in 214 children, showed significant differences in RBM thickness between children with mild–moderate asthma and SUA. The same study showed a reverse correlation between RBM thickness and FEV1 confirming the relationship between airway remodeling and pulmonary function deterioration, which is particularly worrisome considering the evolving data which suggests there is a major role of childhood SUA in the development of chronic obstructive pulmonary disease (COPD) later in life [57]. Importantly, airway remodeling does not seem to be present in all children with SUA. RBM thickening was shown in only 57% of 24 pediatric patients with SUA [47]. It correlates with the notion that airway remodeling is more likely to occur with Th2 endotype and less likely with non-type-2 endotype of SUA [58].

Considering all the above, the assessment of airway remodeling via measurement of RBM thickness in EBB is an important part of the assessment of SUA. Its presence should alert the asthma practitioner to the potential for lung function deterioration and, as it will be shown below, provides the incentive for specific treatment.

Bacterial Lower Airway Infection and Inflammation in Asthma

During the last two decades of asthma research, there has been a remarkable shift of the paradigm of understanding of the pathogenesis and immunology of asthma. Traditionally, most of the pediatric asthma researchers have been focusing on respiratory viruses; however, more recently more attention is paid to the role of bacteria in the development and persistence of asthmatic inflammation of the airway and asthma exacerbations [59].

The Copenhagen Prospective Study on Asthma in Childhood birth cohort enrolled 321 neonates and followed them until 5 years of age in order to investigate a possible association between bacterial colonization of the hypopharynx in asymptomatic neonates and later development of recurrent wheeze and asthma. Neonates colonized in the hypopharyngeal region with *S. pneumonia*, *H. influenza*, or *M. catarrhalis*, or with a combination of these organisms, were at increased risk for recurrent wheeze and asthma early in life (Fig. 24.4). *H. influenzae* colonization carried a particularly high adjusted hazard

Table 1. Hazard Ratios for the Presence of Bacteria in Cultures from Airways at 1 Month of Age in Relation to Primary End Points.

End Point and Bacterial Species	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)*
First wheezy episode		
Streptococcus pneumoniae	1.54 (1.02–2.31)	1.53 (0.97–2.40)
Haemophilus influenzae	1.49 (1.00–2.22)	1.27 (0.82–1.97)
Moraxella catarrhalis	1.83 (1.20–2.78)	1.76 (1.08–2.85)
Staphylococcus aureus	1.03 (0.80–1.32)	0.97 (0.74–1.26)
At least one of *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*	1.65 (1.24–2.21)	1.50 (1.08–2.10)
Persistent wheeze		
S. pneumoniae	1.71 (0.85–3.45)	1.41 (0.65–3.07)
H. influenzae	2.85 (1.52–5.33)	2.73 (1.36–5.48)
M. catarrhalis	2.19 (1.12–4.28)	1.53 (0.72–3.25)
S. aureus	1.04 (0.63–1.71)	1.00 (0.59–1.68)
At least one of *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*	2.40 (1.45–3.99)	2.01 (1.13–3.57)
Acute severe exacerbation of wheeze		
S. pneumoniae	1.80 (0.80–4.02)	2.02 (0.79–5.17)
H. influenzae	3.23 (1.60–6.52)	3.78 (1.70–8.40)
M. catarrhalis	2.72 (1.27–5.84)	2.52 (0.92–5.51)
S. aureus	1.01 (0.56–1.82)	1.09 (0.58–2.05)
At least one of *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*	2.99 (1.66–5.39)	3.14 (1.57–6.30)
Hospitalization for wheeze		
S. pneumoniae	1.90 (0.73–4.94)	2.33 (0.72–7.54)
H. influenzae	3.81 (1.70–8.51)	4.09 (1.65–10.15)
M. catarrhalis	3.68 (1.58–8.54)	2.93 (1.06–8.11)
S. aureus	1.18 (0.57–2.46)	1.32 (0.58–2.99)
At least one of *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*	3.85 (1.90–7.79)	3.57 (1.55–8.23)

* Hazard ratios were adjusted for the following possible confounders: sex, gestational age at birth, maternal smoking during the third trimester, maternal use of antibiotics during the third trimester, breast-feeding, lung function, bronchial responsiveness, and the presence or absence of older children at home.

Fig. 24.4 From Bisgaard et al. [60]

ratio for persistent and severe wheezing. The prevalence of asthma and the reversibility of airway resistance after beta-2 agonist administration at 5 years of age were significantly increased in the children colonized neonatally with these organisms. In addition, the percentage change in blood eosinophil count and IgE increased significantly with age in children who were colonized [60]. This raised major interest in the potential role of bacterial pathogens in pediatric asthma pathogenesis.

Apparently, the biggest question is related to the role of bacterial pathogens in BAL neutrophilia, which is often observed in children with asthma and interpreted as "neutrophilic asthma phenotype." In one study, bacterial infection in BAL was found in 78 children with wheezing not associated with airway abnormalities. They had a significantly higher percentage of neutrophils compared with children with no bacteria in their BAL [9], which correlated well with the data from an adult study, which suggested that BAL neutrophilia and "neutrophilic phenotype" may result from "subclinical airway infection" in certain patients with SUA [61]. Similarly, the researchers from Pediatric Severe Asthma Molecular Phenotype cohort [44] described a cluster of 138 children with SUA with "neutrophilic steroid-refractory recurrent wheezing," which was characterized by a higher blood neutrophil count, presence of more nonallergic comorbidities, such as history of pneumonia (31%, $P < 0.001$), and more frequent history of GERD (37%, $P < 0.001$), than children of the other clusters of asthma. The BAL bacterial cultures were significantly more positive (26%, $P < 0.001$) in this cluster, with a predominance of *Haemophilus influenzae* and *Moraxella catarrhalis*. Despite the suggestive role of bacteria in SUA, it has to be acknowledged that the concept of "neutrophilic asthma in the absence of infection" has been known for many years. Its mechanism is poorly understood and is often explained by the "proinflammatory state" of asthmatic neutrophils, which are capable of releasing neutrophil activation factors such as myeloperoxidase, elastase, and lactoferrin protein in the airway [62]. However, the recent advances of airway microbiome research allow for a different and, probably, more logical explanation. It was shown by Segal et al. [63] that enrichment of BAL with supraglottic taxa, such as *Veillonella* and *Prevotella*, results in increased pulmonary inflammation including increased BAL neutrophil counts. Kazachkov et al. [64] studied lower airway microbiome in the cohort of pediatric patients with persistent pulmonary symptoms and showed that asthmatic subjects had significant BAL neutrophilia and their lower airway microbiome tended to be in close proximity to and related to oral commensal bacteria. A greater dissimilarity between the upper airway and lower airway microbiota was found in children with bacterial bronchitis and aspiration, who had more prominent effect of environmental bacteria in the development of their lower airway inflammation. It was shown that the presence of purulent bronchial secretions, which could be quantitated by assigning bronchial secretions grade [65] during bronchoscopy, is strongly suggestive of BAL neutrophilia and active bacterial infection confirmed by both traditional BAL culturing [66] and 16S sequencing technique [64]. In general, the presence of purulent bronchial secretions and a high bronchial secretions grade above 3 [66] has to be considered as suggestive of active bacterial bronchitis even in the absence of confirmatory BAL culture, particularly considering very low accuracy of traditional BAL culture in characterizations of lower airway microbiota compared with 16S sequencing methods [64]. Taking into consideration all of the above, it has to be suggested that BAL neutrophilia, which is often interpreted as "neutrophilic phenotype" in asthmatic patients, may be explained by high bacterial load of the lower airway even in the absence of positive BAL cultures. Also, it was shown that pretreatment enrichment in certain asthma-associated genre, such as *Haemophilus,* detected by 16S sequencing method, is associated with diminished response to inhaled corticosteroids [67], which may link "severe neutrophilic asthma phenotype" to lower airway overgrowth of certain bacteria, which could be easily missed by traditional culture methods.

It is important to mention that clinical coexistence of suppurative lung disease and asthma is well known to asthma practitioners. There are

several studies describing the occurrence of bronchiectasis in asthmatic patients [68–70], which created the term "asthma-bronchiectasis overlap," which is now used in adult literature. Presence of bronchiectasis was associated with an increased frequency of exacerbations, emergency room visits, and greater use of systemic corticosteroids compared with asthmatic control subjects without bronchiectasis [71]. Despite the presence of a well-established link, the causal relationship between the two conditions is not well understood and it remains unknown whether "asthma-bronchiectasis overlap" represents another phenotype of asthma. There are data, which suggest that treatment of bacterial lower airway infections may significantly improve asthma symptoms in adults; it will be reviewed later in this chapter.

The concept of bacterial infection in early childhood wheezing and asthma has been discussed in the pediatric literature too. ATS Committee Statement on Diagnostic Evaluation of Infants with Recurrent or Persistent Wheezing literature came to the conclusion that 20–30% of children with persistent wheezing who undergo bronchoscopy with BAL will be found to have a lower airway bacterial infection and that their symptoms will improve with antibiotic therapy [16]. There are very few published pediatric studies on the association of asthma with suppurative lung disease in older children. There is an indication of the role of asthmatic lower airway inflammation and mucous plugging in the development of right middle lobe syndrome, an important cause of pediatric bronchiectasis [72]. There is a suggested overlap of the most common suppurative lung disease of childhood, protracted bacterial bronchitis (PBB), with asthma [73]. Interestingly, Kinghorn et al. [74] recently showed that physician-diagnosed asthma was the most common comorbidity and was present in 80% of the group of Alaska native children with bronchiectasis. Finally, in the previously cited study [47], bacterial bronchitis with positive BAL cultures ($\geq 10^4$ cfu/ml) was found in 54% of studied patients with SUA.

In conclusion, bacterial lower airway infection plays an important role in the pathogenesis and clinical phenotype of asthma. Pediatric studies will be required to establish proper pathways to their diagnostics and treatment.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a major complicating factor for SUA in adults [75, 76]. Patients with SUA and ABPA require a very different approach to their pulmonary disease with the administration of long-term treatments with systemic steroids and antifungal agents. Agarwal et al. [77] suggested the diagnostic algorithm for the diagnosis of ABPA in adults with SUA, which is based on detection of high levels of IgE, elevated IgE and IGG antibodies to Aspergillus, elevated eosinophilic count, as well as typical radiographic findings of bronchiectasis and attenuated mucus on computer tomography of the chest.

ABPA is a well-known comorbidity in children with cystic fibrosis [78], but its prevalence and role in pediatric asthma have not been defined with the overall impression being that ABPA very infrequently complicates pediatric asthma. However, with higher awareness of the condition and vigorous application of diagnostic criteria, this impression may soon change. Apparently, ABPA may complicate SUA in children starting at a young age [79]. In the study by Singh et al. [80], ABPA was diagnosed in 26 of 100 studied pediatric patients with SUA. The authors applied immunological and radiological criteria to the diagnosis but came up with a higher than usual cut-off point for total IgE, 1200 IU/ml, which was proposed as a predictive parameter for ABPA in children with asthma after post hoc analysis. They also reported that a relatively low amount of pediatric patients with SUA and ABPA in their cohort (15%) had elevated IgG precipitating antibody.

Aspergillus hyphae were recovered from BAL [81] and even from biopsy sample [82] of children with ABPA and cystic fibrosis; however, microbiological methods do not seem to be contributory to

ABPA diagnosis [83]. The galactomannan index shown previously to be valuable in the detection of invasive pulmonary aspergillosis [84] does not seem to perform well in adult patients with ABPA [85] and its value in pediatric SUA has not been established. There are evolving data on the application of PCR for the detection of Aspergillus in respiratory secretions in patients with ABPA. In one of the adult studies, PCR positive sputum samples were found in 50% of patients with ABPA compared with 3% of controls [86]. There are no data on the application of PCR in BAL of children with ABPA yet; however, it may become a helpful practical tool in the future.

Bronchoscopy may be therapeutic in patients with ABPA. In certain cases, the removal of mucous plugs and aggressive bronchoscopic bronchial toilette may serve as a useful adjunct to treatments providing improvement in symptoms and lung function [87] and even reducing IgE levels [88].

Flexible Bronchoscopy in Defining SUA Phenotypes

SUA results from a complex interaction of multiple factors, which include genetics, structural, functional, patient-related, and others which are usually referred to as "asthma phenotype." Asthma endotype is usually defined as complex characteristics of immunity of airway inflammation [89]. Phenotyping and endotyping of SUA is extremely valuable because it provides necessary information on the clinical presentation, as well as etiology, type, and quantity of lower airway inflammation and gives important leads to its successful management [90]. It has to be mentioned that the terms "phenotype," "endotype," "sub-phenotype," and "clinical phenotype" have been used in asthma literature sometimes interchangeably, which may create confusion. That is why, for practical purposes, in this chapter, we have been using the term "phenotype" for defining the association of certain clinical, microbiological, and histological patterns in patients with SUA.

An important study by Good et al. [91] attempted to develop practically sound, bronchoscopy-based phenotypes of SUA in adults. Fifty-eight patients meeting the ATS definition of severe asthma underwent bronchoscopy with bronchoalveolar lavage and endobronchial biopsy and brushing. Five phenotypes were generated, based on bronchoscopic evaluation and additional methods of investigations, and included gastroesophageal reflux (GER), subacute bacterial infection, tissue eosinophilia, combination, and nonspecific. Targeted interventions depended on the phenotype assigned to the patient and included antireflux medications, antibiotics directed against specific pathogens recovered from BAL, omalizumab for severe tissue eosinophilia, or some combination of the above. After 12–60 weeks of targeted specific therapy for the entire group, there was a significant improvement in the ACT score (pretest, 11.6 ± 4.1; posttest, 18.5 ± 4.1; $P < 0.001$) and FEV1% predicted (pretest, 58.9 ± 17.0%; posttest, 74.3 ± 15.2%; $P < 0.001$) (Fig. 24.5).

Despite the fact that the above study was done on adults and its results cannot be readily extrapolated to pediatric patients, there are certain important practical considerations, which could be presented here. Application of pediatric bronchoscopy, BAL, and EBB to children with SUA allows for assigning distinctive bronchoscopy-based phenotypes in a somewhat similar manner to those described by Good et al. [91], while also taking into consideration the current understanding of pathology and complicating factors of SUA in children. We would like to attempt to present this bronchoscopy-based classification with suggestions for potential targeted interventions here.

Persistent Airway Eosinophilia Phenotype

Airway eosinophilia often persists in children with SUA despite aggressive and long-term therapy with ICS [43, 47]. As it was discussed previously in this chapter, severe eosinophilic phenotype is associated with refractory asthma symptoms and can be reliably diagnosed with

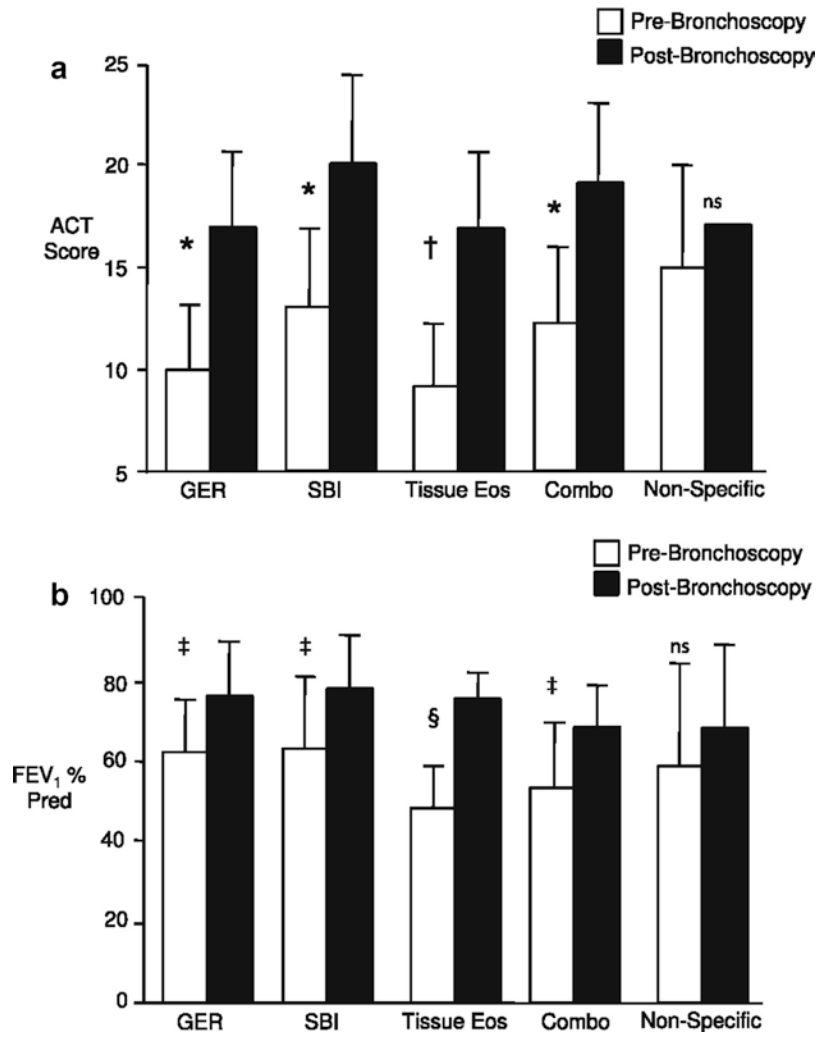

Fig. 24.5 Pre-bronchoscopy on standard therapy and post-bronchoscopy with specific directed therapy From Good et al. [91]

detection of eosinophils in BAL and EBB with a clear understanding of the importance of EBB and insufficiency of BAL alone for assessment of airway eosinophilia [43, 44, 47, 92]. Previously cited, Good et al. [91] used omalizumab as the main treatment option for adults with SUA and tissue eosinophilia. It resulted in a reduction of symptoms and improvement of FEV1 in this group of patients. Omalizumab is advanced humanized IgG1 monoclonal anti-IgE antibody specifically designed to bind circulating free IgE and is shown to be effective in children with SUA aged 6 years and above [93]. Adolescents with higher peripheral and sputum eosinophilic counts are more likely to respond well to therapy with omalizumab [94]. It was also shown that omalizumab is capable of reducing endobronchial eosinophils in patients with SUA [95]. Over the last decade, several biological drugs capable of directly reducing systemic and pulmonary eosinophilia became available to pediatrics. Mepolizumab, a humanized monoclonal antibody against interleukin-5, was shown to be clinically effective in eosinophilic asthma [96]. It was shown to have potent anti-eosinophil effects leading to dramatic reduction in airway eosinophilia in adult patients with asthma undergoing segmental allergen challenge test [97]. Mepolizumab has a good safety profile and is approved for use in children [98]. Another promising drug is benralizumab, a potent biologic targeting the IL-5 receptor on eosinophils and basophils leading to

depletion of target cells in peripheral blood and tissues, which is approved in children age 12 years and above [99]. Its good safety profile and efficacy during once in 8 weeks administration make it an attractive treatment option for children with SUA and persistent airway eosinophilia [100].

Thus, the addition of biologicals to the management schedule of children with persistent eosinophilia phenotype of SUA seems to be practically feasible. It has to be stated, though, that the selection of cut-off value for airway eosinophils for initiation of biological therapy in children with SUA is difficult. The cut-off point of ≥10 tissue eosinophils per HPF was used in adults with SUA [91]; however, this number was chosen merely arbitrary by the authors. The pediatric studies showed that children with SUA have median BAL eosinophils of 2.4% [43] and median EBB eosinophils of 5 per HPF [101] despite treatment with high dose of ICS prior to assessment. Although those findings do not validate those numbers as the cut-off for biological therapy, it does makes them eligible as an arbitrary suggestion. In the author's opinion, the decision on initiation of biological therapy in children with SUA has to be made on an individual basis after considering the combination of clinical symptoms and the presence of persistent airway eosinophilia.

Airway Remodeling Phenotype

As it was discussed earlier in this chapter, airway remodeling occurs frequently in children with SUA and may be associated with rapid deterioration of lung function [43, 52, 56] as well as the development of COPD later in life [57], and finding of thickened RBM during EBB suggests the presence of airway remodeling. Data from adult studies show that airway remodeling can be successfully managed, judged by a significant reduction of RBM after treatment with ICS [102–105]. This successful strategy was mostly reported with prolonged use of very high doses of ICS and has to be used with caution in pediatric patients only after careful assessment of the risk to benefit ratio of this treatment. It is somewhat reassuring that treatment with very high doses of ICS (equivalent to 500–1000 mcg/day of fluticasone propionate or 1000–2000 mcg/day of budesonide for a period of at least 12 months) did not substantially affect adrenal function in children with SUA in one of the published studies [106], which, certainly, shall not prevent asthma practitioners from careful monitoring for side effects during treatment with very high doses of ICS.

Anti-inflammatory properties of macrolide antibiotics and particularly azithromycin have been studied extensively. Experimental studies on the murine model of asthma showed that azithromycin may ameliorate airway remodeling via inhibiting several inflammatory pathways and airway apoptosis [107–109]. Taking into account the relative safety of azithromycin and other macrolides and their efficacy in the treatment of other pediatric pulmonary conditions associated with severe airway inflammation and airway remodeling such as cystic fibrosis (CF) and non-CF bronchiectasis [110–112], it may become an attractive option for add-on therapy in children with SUA and airway remodeling phenotype. It has to be stated that objective qualitative assessment of RBM thickness is elaborate [113] and has been used mostly for research-related purposes. Practically, this assessment is qualitative and depends on the expertise of the pediatric pathologist, which makes it somewhat less objective. Also, direct assessment of success of any treatment of airway remodeling would require repeated EBB with measurement of RBM thickness in children with airway remodeling phenotype of SUA, which may not be feasible due to ethical considerations. However, follow up on clinical presentation and pulmonary function may provide an indirect measure for treatment efficacy in a subset of children with airway remodeling phenotype of SUA.

SUA/Bacterial Bronchitis Overlap Phenotype

The contribution of bacterial lower airway infection to the pathogenesis and clinical presentation of SUA had been reviewed here earlier [59, 60, 64].

The antibacterial agents, which have been extensively studied for their potential use in

asthma, are macrolide antibiotics. A 2013 meta-analysis of 12 randomized, controlled trials of macrolides for the long-term management of asthma in both adults and children found positive effects on peak expiratory flow rate, asthma symptoms, asthma quality of life, and airway hyper-responsiveness [114]. More recently, it was shown to reduce asthma exacerbations in patients with SUA [115]. These beneficial effects have been attributed to both anti-inflammatory and antibacterial properties of macrolide antibiotics with special emphasis of their efficiency against *Mycoplasma pneumoniae* and *Chlamydia pneumonia* infections, which are considered to be contributory to the development of SUA in certain patients [116]. The advances in microbiome research allow for a deeper understanding of the role of azithromycin in SUA. Azithromycin therapy was associated with decreased bacterial richness and reduction of *Pseudomonas*, *Haemophilus*, and *Staphylococcus* detected via DNA sequencing in the BAL of patients with severe asthma [117], which may indirectly explain its ability to reduce airway neutrophil infiltration in some asthmatic children [118].

Azithromycin prophylactic treatment was also shown to be effective in reducing exacerbations of non-CF bronchiectasis and suppurative lung disease in children [119], which also emphasizes its important role as an adjunctive therapeutic agent in patients with suppurative lung disease associated with SUA in adults and children [68, 69, 107].

Unfortunately, much less is known in the application of nonmacrolide antibiotics to the management of SUA. The indications for appropriate therapy of acute and chronic airway infection as well as protocols for long-term treatments with systemic and inhaled antibiotics in pediatric patients with SUA/bacterial bronchitis overlap still have to be defined [70]. It is very hard to argue, though, that antibacterial therapy should be considered every time when purulent bronchitis and/or heavy bacterial load in the lower airways are detected during bronchoscopy with BAL.

SUA/Esophagitis Phenotype

The causal relationship of gastroesophageal reflux (GER) to asthma in children is a controversial topic. However, proven GER is acknowledged as an important complicating factor in the management of SUA in children and adults [31]; furthermore, reflux-esophagitis (ReE) has been strongly associated with increased airway hyperreactivity [120]. Despite this knowledge, there is no clear indication that the treatment of ReE improves clinical symptoms or pulmonary function in children and adults with asthma [121]. On the other hand, this treatment still may provide benefit to certain selected patients with SUA and ReE. It was shown previously that treatment of ReE improves peak expiratory flow rate in the subgroup of adults with SUA and severe esophagitis characterized by profound esophageal mucosal break [122]. Furthermore, aggressive treatment of "GER-severe asthma phenotype" was shown to be beneficial in a cohort of adult patients with SUA in the previously cited study [91].

Over the last several years, the concept of eosinophilic esophagitis (EoE) and its relationship to respiratory disease in children has been emerging [123]. It was noticed that despite distinctive differences in pathology, both ReE and EoE are characterized by the presence of esophageal eosinophils [124]. Recently, Erkman et al. [47] reported that elevated esophageal eosinophils were found in 11 (46%) of studied children with SUA. There was a correlation between the presence of EoE and GI symptoms, such as abdominal pain, vomiting, choking with food ($R = 0.45$, $P = 0.027$) as well as with food allergies ($R = 0.45$, $P = 0.028$). Presence of airway eosinophils correlated with esophageal eosinophils ($R = 0.41$, $P = 0.047$). It was shown previously that treatment with proton pump inhibitors (PPI) improves esophageal eosinophilia in 68% and completely resolves it in 47% of children [125]; however, due to complete absence of data, it is unclear whether this reduction of esophageal eosinophilia improves clinical and functional characteristics of SUA

in patients with combined airway and esophageal eosinophilia.

There are striking similarities in the pathogenesis and pathology of eosinophilic asthma and eosinophilic esophageal disease suggested previously [126, 127], which raises the possibility of a "common treatment" concept for these two conditions. Biological anti-eosinophilic agents have been successfully used in children with SUA [98–100]. There are emerging data on their potential use in patients with esophageal eosinophilia. The current literature indicates that therapeutic agents targeting IL-5 have demonstrated reductions in esophageal eosinophilic inflammation. An international, multicenter, double-blind randomized trial investigated the effect of mepolizumab, anti-IL-5 monoclonal immunoglobulin G1 antibody in pediatric EoE and showed significant, although not curative, reduction of esophageal eosinophilic inflammation after three injections [128]. Recently, it was shown that benralizumab, IL-5 receptor antagonist with enhanced antibody-dependent cell-mediated toxicity, is clinically and histologically effective in the treatment of severe gastrointestinal eosinophilia [129]. To the author's knowledge, there are no published reports on the biological treatment of patients with a combination of severe eosinophilic asthma and EoE; however, the above-reviewed data make this approach potentially attractive in patients with aerodigestive eosinophilia. Although the presented data cannot ultimately recommend an aerodigestive approach with a combination of bronchoscopy, BAL, EBB, and EGD with biopsies for evaluation of SUA, overall, it has to be considered in certain patients with clinical features consistent with esophagitis and food allergies.

Suggestions on the Practical Approach to SUA Management Based on Bronchoscopy Findings

It has to be emphasized that most of children with SUA cannot be easily assigned to one of bronchoscopy-based phenotypes, but present with mixed features, which overlap and, possibly, contribute to each other. Combination of airway neutrophilia with eosinophilia [92], airway neutrophilia with bacterial infection [9], airway eosinophilia with airway remodeling [105], and aerodigestive eosinophilia with bacterial airway infection [47] was acknowledged previously. In addition, as it was discussed earlier in this chapter, certain patients with SUA have anatomical airway abnormalities, which may contribute to the severity of their presentation [9, 16, 17]. That is why the management plan of children with SUA has to be based on an analysis of multiple clinical, functional, and bronchoscopic features and findings.

Considering this, the author would like to make practical suggestions, which would outline the role of flexible bronchoscopy in creating individualized management plans for children with SUA (Tables 24.1 and 24.2 and Fig. 24.6).

The author has to acknowledge, though, that a "bronchoscopy-based" approach to SUA has not been sufficiently studied in pediatrics and the practical suggestions presented below are based on a combination of reviewed published data, personal experience, and common sense.

In conclusion, flexible bronchoscopy has to be strongly considered in children with SUA, because it improves understanding the nature of SUA in individual patients and provides pathways to targeted treatments. The approach to SUA management has to be complex and needs to take into consideration the whole association of clinical, physiological, anatomical, microbiological, cytological, and histological factors. Prospective pediatric research studies will be required to prove that bronchoscopy-based individualized approach to diagnostics and treatment is valid and efficient in the management of SUA in children.

Acknowledgment The author wants to express his deep gratitude to his co-worker and friend, Ms. Jessica Erkman, CPNP for her ongoing collaboration and help with preparing of this chapter.

Table 24.1 Suggestions for performing bronchoscopy in children with SUA

1.	Flexible bronchoscopy has to be considered in children with SUA if the asthma practitioner is unable to achieve control of asthma symptoms and exacerbations, and/or is unable to prevent deterioration of pulmonary function despite maximizing asthma control medications, addressing complicating factors and adherence
2.	Flexible bronchoscopy should be performed by an experienced pediatric bronchologist capable of identifying anatomical airway abnormalities, including tracheomalacia and EDAC, as well as, performing endobronchial biopsy
3.	Rigid laryngoscopy may be considered in order to evaluate for laryngeal cleft.
4.	It is suggested that BAL is performed in every patient undergoing bronchoscopy for SUA. BAL fluid has to be sent for cell count and differential and bacterial culture. Fungal culture and Aspergillus galactomannan[a] may be added when ABPA is suspected
5.	It is suggested that EBB is performed in every patient undergoing bronchoscopy for SUA. The specimens have to be evaluated by a qualified anatomic pathologist for airway remodeling features, presence of acute and chronic airway inflammation with characterization of predominant inflammatory cells, and quantification of eosinophils per HPF
6.	It is suggested that EGD is considered in patients undergoing bronchoscopy for SUA, particularly when they have GI symptoms such as abdominal pain, vomiting, and choking with feeds and/or severe food allergies. Biopsy specimens have to be evaluated by an anatomic pathologist for features consistent with ReE, EoE, and esophageal eosinophilia

[a]*Validity of Aspergillus galactomannan in pediatric SUA has not been established*

Table 24.2 Suggestions for alteration of management of SUA in children based on bronchoscopic findings

1.	Presence of significant anatomical airway abnormalities (tracheomalacia, EDAC, laryngeal cleft) has to be acknowledged and proper management has to be suggested
2.	The following features are suggested to be consistent with presence of bacterial lower airway inflammation. Antibacterial treatment and long-term azithromycin[a] may be considered
	a. Presence of purulent secretions with high bronchial secretions grade (BS grade) of 5 and 6
	b. Presence of positive quantitative BAL bacterial culture and BAL neutrophilia ≥5% [38]
3.	The following values[b] are suggestive of persistent airway eosinophilia in patients with SUA. Treatment with biologicals may be considered
	a. BAL eosinophils >2.7%
	b. EBB eosinophils >5 per HPF
4.	Presence of increased RBM thickness may be suggestive of airway remodeling[c]. Treatment with very high dose of ICS, long-term azithromycin[a], and biologicals may be considered in patients with irreversible moderate–severe lower airway obstruction
5.	Presence of histological features consistent with ReE and EoE diagnosed after EGD with biopsies in children with SUA is suggestive of initiation of appropriate therapy[d]

[a]*Efficacy of long-term prophylactic treatment with azithromycin in children with SUA has not been established*
[b]*These are arbitrary values, please see the related discussion in "Persistent airway eosinophilia phenotype" chapter section*
[c]*Assessment of RBM thickness may be subjective, please see the related discussion in "Airway remodeling phenotype"*
[d]*There are no published studies suggesting that treatment of ReE and EoE improves SUA in children*

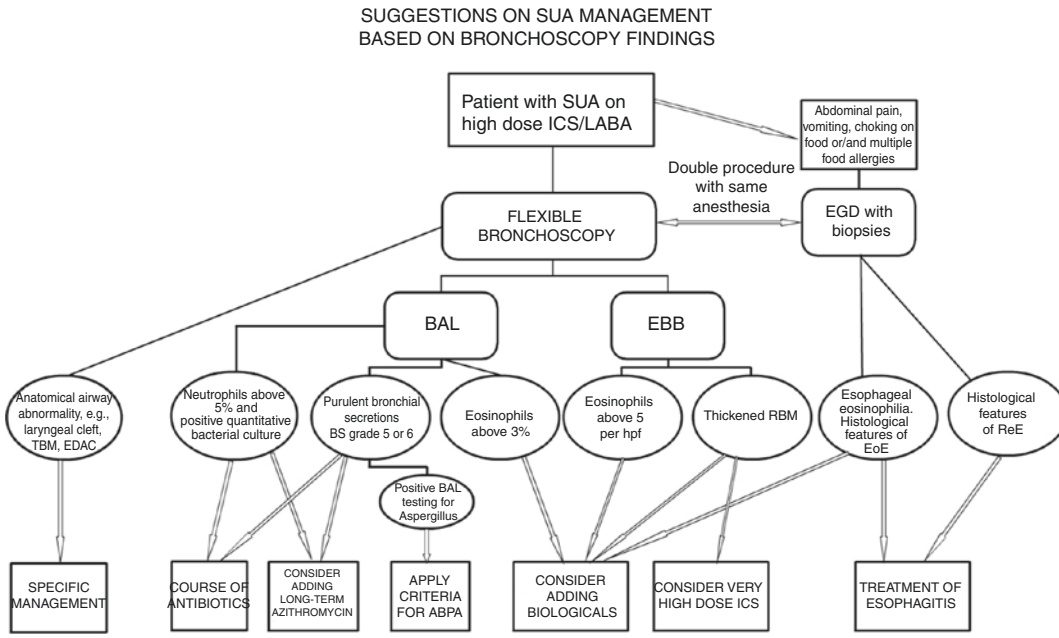

Fig. 24.6 Suggestions on SUA management based on bronchoscopy findings. (Original figure by M. Kazachkov)

References

1. Smith A, Serban N, Fitzpatrick A. -Asthma Prevalence Among Medicaid-Enrolled Children. The journal of allergy and clinical immunology In practice. 2018;7(4):1207–13
2. Schramm D, Yu Y, Wiemers A, Vossen C, Snijders D, Krivec U, et al. Pediatric flexible and rigid bronchoscopy in European centers-availability and current practice. Pediatr Pulmonol. 2017;52(11): 1502–8.
3. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31:143–78. The European Respiratory Journal. 2018;51(2)
4. Moore WC, Evans MD, Bleecker ER, Busse WW, Calhoun WJ, Castro M, et al. Safety of investigative bronchoscopy in the severe asthma research program. J Allergy Clin Immunol. 2011;128(2):328–36.e3.
5. Payne D, McKenzie SA, Stacey S, Misra D, Haxby E, Bush A. Safety and ethics of bronchoscopy and endobronchial biopsy in difficult asthma. Arch Dis Child. 2001;84(5):423–6.
6. Jackson C. Bronchoscopy, Esophagoscopy and gastroscopy. 3d ed. Philadelphia: W.B Saunders Company; 1934. p. 166.
7. de Benedictis FM, de Benedictis D, Mirabile L, Pozzi M, Guerrieri A, Di Pillo S. Ground zero: not asthma at all. Pediatr Allergy Immunol. 2015;26(6):490–6.
8. Payne DN, Lincoln C, Bush A. Lesson of the week: right sided aortic arch in children with persistent respiratory symptoms. BMJ (Clinical Research ed). 2000;321(7262):687–8.
9. Gu W, Jiang W, Zhang X, Chen Z, Yan Y, Huang L, et al. Refractory wheezing in Chinese children under 3 years of age: bronchial inflammation and airway malformation. BMC Pediatr. 2016;16(1):145.
10. Kryger M, Bode F, Antic R, Anthonisen N. Diagnosis of obstruction of the upper and central airways. Am J Med. 1976;61(1):85–93.
11. Kusak B, Cichocka-Jarosz E, Jedynak-Wasowicz U, Lis G. Pulmonary function tests leading to the diagnosis of vascular malformations in school-aged children. Adv Respirat Med. 2017;85(5):253–7.
12. Mappa L, Cardinale F, Camodeca R, Tortorella ML, Pietrobelli A, Armenio L, et al. Exaled nitric oxide and air trapping correlation in asthmatic children. Allergy. 2005;60(11):1436–9.
13. Lee EY, Tracy DA, Bastos M, Casey AM, Zurakowski D, Boiselle PM. Expiratory volumetric MDCT evaluation of air trapping in pediatric patients with and without tracheomalacia. AJR Am J Roentgenol. 2010;194(5):1210–5.
14. Klein M. Respiratory problems in: handbook of pediatrics Ed Motal C. 7th ed. Cape Town: Oxford University Press; 2010.

15. White DA, Zar HJ, Madhi SA, Jeena P, Morrow B, Masekela R, et al. Acute viral bronchiolitis in South Africa: diagnostic flow. South Afr Med J (Suid-Afrikaanse tydskrif vir geneeskunde). 2016;106(4):25–6.
16. Ren CL, Esther CR Jr, Debley JS, Sockrider M, Yilmaz O, Amin N, et al. Official American Thoracic Society clinical practice guidelines: diagnostic evaluation of infants with recurrent or persistent wheezing. Am J Respir Crit Care Med. 2016;194(3):356–73.
17. Boesch RP, Baughn JM, Cofer SA, Balakrishnan K. Trans-nasal flexible bronchoscopy in wheezing children: diagnostic yield, impact on therapy, and prevalence of laryngeal cleft. Pediatr Pulmonol. 2018;53(3):310–5.
18. Hernandez Arauzo N, Castillo Marchuet MJ, Vinas Domingo M, Ibero Iborra M. Tracheomalacia: uncommon onset in a patient with severe asthma. J Investig Allergol Clin Immunol. 2011;21(5):412–3.
19. Kalra A, Abouzgheib W, Gajera M, Palaniswamy C, Puri N, Dellinger RP. Excessive dynamic airway collapse for the internist: new nomenclature or different entity? Postgrad Med J. 2011;87(1029):482–6.
20. Hammond K, Ghori UK, Musani AI. Tracheobronchomalacia and excessive dynamic airway collapse. Clin Chest Med. 2018;39(1):223–8.
21. Feist JH, Johnson TH, Wilson RJ. Acquired tracheomalacia: etiology and differential diagnosis. Chest. 1975;68(3):340–5.
22. Wright CD. Tracheobronchomalacia and expiratory collapse of central airways. Thorac Surg Clin. 2018;28(2):163–6.
23. Hysinger EB, Panitch HB. Paediatric Tracheomalacia. Paediatr Respir Rev. 2016;17:9–15.
24. Panitch HB, Keklikian EN, Motley RA, Wolfson MR, Schidlow DV. Effect of altering smooth muscle tone on maximal expiratory flows in patients with tracheomalacia. Pediatr Pulmonol. 1990;9(3):170–6.
25. Panitch HB, Allen JL, Alpert BE, Schidlow DV. Effects of CPAP on lung mechanics in infants with acquired tracheobronchomalacia. Am J Respir Crit Care Med. 1994;150(5 Pt 1):1341–6.
26. Dave S, Currie BG. The role of aortopexy in severe tracheomalacia. J Pediatr Surg. 2006;41(3):533–7.
27. Shieh HF, Smithers CJ, Hamilton TE, Zurakowski D, Rhein LM, Manfredi MA, et al. Posterior tracheopexy for severe tracheomalacia. J Pediatr Surg. 2017;52(6):951–5.
28. Ernst A, Majid A, Feller-Kopman D, Guerrero J, Boiselle P, Loring SH, et al. Airway stabilization with silicone stents for treating adult tracheobronchomalacia: a prospective observational study. Chest. 2007;132(2):609–16.
29. Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, De Benedictis FM, Melen E, et al. Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. Eur Respir J. 2010;36(1):196–201.
30. Pike KC, Levy ML, Moreiras J, Fleming L. Managing problematic severe asthma: beyond the guidelines. Arch Dis Child. 2018;103(4):392–7.
31. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet L-P, Brightling C, Chanez P, Dahlen S-E, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343–73. The European Respiratory Journal. 2018;52(1)
32. Lang A, Carlsen KH, Haaland G, Devulapalli CS, Munthe-Kaas M, Mowinckel P, et al. Severe asthma in childhood: assessed in 10 year olds in a birth cohort study. Allergy. 2008;63(8):1054–60.
33. Chipps BE, Szefler SJ, Simons FE, Haselkorn T, Mink DR, Deniz Y, et al. Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. J Allergy Clin Immunol. 2007;119(5):1156–63.
34. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol. 2004;113(1):101–8.
35. Payne DN, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. Am J Respir Crit Care Med. 2001;164(8 Pt 1):1376–81.
36. Lex C, Ferreira F, Zacharasiewicz A, Nicholson AG, Haslam PL, Wilson NM, et al. Airway eosinophilia in children with severe asthma: predictive values of noninvasive tests. Am J Respir Crit Care Med. 2006;174(12):1286–91.
37. Korevaar DA, Westerhof GA, Wang J, Cohen JF, Spijker R, Sterk PJ, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. Lancet Respir Med. 2015;3(4):290–300.
38. Ratjen F, Bredendiek M, Brendel M, Meltzer J, Costabel U. Differential cytology of bronchoalveolar lavage fluid in normal children. Eur Respir J. 1994;7(10):1865–70.
39. Fitch PS, Brown V, Schock BC, Taylor R, Ennis M, Shields MD. Chronic cough in children: bronchoalveolar lavage findings. Eur Respir J. 2000;16(6):1109–14.
40. Allen JN, Davis WB, Pacht ER. Diagnostic significance of increased bronchoalveolar lavage fluid eosinophils. Am Rev Respir Dis. 1990;142(3):642–7.
41. Snijders D, Agostini S, Bertuola F, Panizzolo C, Baraldo S, Turato G, et al. Markers of eosinophilic and neutrophilic inflammation in bronchoalveolar lavage of asthmatic and atopic children. Allergy. 2010;65(8):978–85.
42. O'Brien CE, Tsirilakis K, Santiago MT, Goldman DL, Vicencio AG. Heterogeneity of lower airway

inflammation in children with severe-persistent asthma. Pediatr Pulmonol. 2015;50(12):1200–4.
43. Bossley CJ, Fleming L, Gupta A, Regamey N, Frith J, Oates T, et al. Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. J Allergy Clin Immunol. 2012;129(4):974–82.e13.
44. Guiddir T, Saint-Pierre P, Purenne-Denis E, Lambert N, Laoudi Y, Couderc R, et al. Neutrophilic steroid-refractory recurrent wheeze and eosinophilic steroid-refractory asthma in children. J Allergy Clin Immunol Pract. 2017;5(5):1351–61.e2.
45. Saglani S, Nicholson AG, Scallan M, Balfour-Lynn I, Rosenthal M, Payne DN, et al. Investigation of young children with severe recurrent wheeze: any clinical benefit? Eur Respir J. 2006;27(1):29–35.
46. Djukanovic R, Wilson JW, Britten KM, Wilson SJ, Walls AF, Roche WR, et al. Quantitation of mast cells and eosinophils in the bronchial mucosa of symptomatic atopic asthmatics and healthy control subjects using immunohistochemistry. Am Rev Respir Dis. 1990;142(4):863–71.
47. Erkman J, Vaynblat A, Thomas K, Segal LN, Levine J, Moy L, et al. Airway and esophageal eosinophils in children with severe uncontrolled asthma. Pediatric pulmonology. 2018;53(12):1598–03
48. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med. 1999;160(3):1001–8.
49. Just J, Bourgoin-Heck M, Amat F. Clinical phenotypes in asthma during childhood. Clin Exp Allergy. 2017;47(7):848–55.
50. Andersson CK, Adams A, Nagakumar P, Bossley C, Gupta A, De Vries D, et al. Intraepithelial neutrophils in pediatric severe asthma are associated with better lung function. J Allergy Clin Immunol. 2017;139(6):1819–29.e11.
51. Jeffery PK. Remodeling and inflammation of bronchi in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2004;1(3):176–83.
52. Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. Eur Respir J. 2007;30(3):452–6.
53. Castro-Rodriguez JA, Saglani S, Rodriguez-Martinez CE, Oyarzun MA, Fleming L, Bush A. The relationship between inflammation and remodeling in childhood asthma: a systematic review. Pediatr Pulmonol. 2018;53(6):824–35.
54. Pohunek P, Warner JO, Turzikova J, Kudrmann J, Roche WR. Markers of eosinophilic inflammation and tissue re-modelling in children before clinically diagnosed bronchial asthma. Pediatr Allergy Immunol. 2005;16(1):43–51.
55. Bonato M, Bazzan E, Snijders D, Tine M, Biondini D, Turato G, et al. Clinical and pathologic factors predicting future asthma in wheezing children. A longitudinal study. Am J Respir Cell Mol Biol. 2018;59(4):458–66.
56. van Mastrigt E, Vanlaeken L, Heida F, Caudri D, de Jongste JC, Timens W, et al. The clinical utility of reticular basement membrane thickness measurements in asthmatic children. J Asthma. 2015;52(9):926–30.
57. Martinez FD. Early-life origins of chronic obstructive pulmonary disease. N Engl J Med. 2016;375(9):871–8.
58. Trejo Bittar HE, Yousem SA, Wenzel SE. Pathobiology of severe asthma. Annu Rev Pathol. 2015;10:511–45.
59. Beigelman A, Rosas-Salazar C, Hartert TV. Childhood asthma: is it all about bacteria and not about viruses? A pro/con debate. J Allergy Clin Immunol Pract. 2018;6(3):719–25.
60. Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bonnelykke K, et al. Childhood asthma after bacterial colonization of the airway in neonates. N Engl J Med. 2007;357(15):1487–95.
61. Alam R, Good J, Rollins D, Verma M, Chu H, Pham TH, et al. Airway and serum biochemical correlates of refractory neutrophilic asthma. J Allergy Clin Immunol. 2017;140(4):1004–14.e13.
62. Grunwell JR, Stephenson ST, Tirouvanziam R, Brown LAS, Brown MR, Fitzpatrick AM. Children with Neutrophil-Predominant Severe Asthma Have Proinflammatory Neutrophils With Enhanced Survival and Impaired Clearance. The journal of allergy and clinical immunology In practice. 2018;7(2):516–25.e6
63. Segal LN, Alekseyenko AV, Clemente JC, Kulkarni R, Wu B, Gao Z, et al. Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. Microbiome. 2013;1(1):19.
64. Kazachkov M, Kapoor BC, Malecha PW, Wu BG, Li Y, Levine J, et al. Aerodigestive dysbiosis in children with chronic cough. Pediatr Pulmonol. 2018;53(9):1288–98.
65. Chang AB, Faoagali J, Cox NC, Marchant JM, Dean B, Petsky HL, et al. A bronchoscopic scoring system for airway secretions--airway cellularity and microbiological validation. Pediatr Pulmonol. 2006;41(9):887–92.
66. Zgherea D, Pagala S, Mendiratta M, Marcus MG, Shelov SP, Kazachkov M. Bronchoscopic findings in children with chronic wet cough. Pediatrics. 2012;129(2):e364–9.
67. Durack J, Lynch SV, Nariya S, Bhakta NR, Beigelman A, Castro M, et al. Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment. J Allergy Clin Immunol. 2017;140(1):63–75.
68. Dimakou K, Gousiou A, Toumbis M, Kaponi M, Chrysikos S, Thanos L, et al. Investigation of bronchiectasis in severe uncontrolled asthma. Clin Respir J. 2018;12(3):1212–8.

69. Oguzulgen IK, Kervan F, Ozis T, Turktas H. The impact of bronchiectasis in clinical presentation of asthma. South Med J. 2007;100(5):468–71.
70. Polverino E, Dimakou K, Hurst J, Martinez-Garcia MA, Miravitlles M, Paggiaro P, et al. The overlap between bronchiectasis and chronic airway diseases: state of the art and future directions. The European respiratory journal. 2018;52(3):1800328
71. Kang HR, Choi GS, Park SJ, Song YK, Kim JM, Ha J, et al. The effects of bronchiectasis on asthma exacerbation. Tubercul Respirat Dis. 2014;77(5):209–14.
72. Priftis KN, Anthracopoulos MB, Mermiri D, Papadopoulou A, Xepapadaki P, Tsakanika C, et al. Bronchial hyperresponsiveness, atopy, and bronchoalveolar lavage eosinophils in persistent middle lobe syndrome. Pediatr Pulmonol. 2006;41(9):805–11.
73. Chang AB, Upham JW, Masters IB, Redding GR, Gibson PG, Marchant JM, et al. Protracted bacterial bronchitis: the last decade and the road ahead. Pediatr Pulmonol. 2016;51(3):225–42.
74. Kinghorn B, Singleton R, McCallum GB, Bulkow L, Grimwood K, Hermann L, et al. Clinical course of chronic suppurative lung disease and bronchiectasis in Alaska Native children. Pediatric pulmonology. 2018;53(12):1662–69
75. Porsbjerg C, Menzies-Gow A. Co-morbidities in severe asthma: clinical impact and management. Respirology (Carlton, Vic). 2017;22(4):651–61.
76. Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. Eur Respir J. 2006;27(3):615–26.
77. Agarwal R, Sehgal IS, Dhooria S, Aggarwal AN. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. Expert Rev Respir Med. 2016;10(12):1317–34.
78. de Almeida MB, Bussamra MH, Rodrigues JC. Allergic bronchopulmonary aspergillosis in paediatric cystic fibrosis patients. Paediatr Respir Rev. 2006;7(1):67–72.
79. Mathur N, Mathur M, Singh V. Youngest case of allergic Broncho pulmonary aspergillosis in India: a case report from arid zone of India. J Clin Diagn Res. 2017;11(4):Od03–od4.
80. Singh M, Das S, Chauhan A, Paul N, Sodhi KS, Mathew J, et al. The diagnostic criteria for allergic bronchopulmonary aspergillosis in children with poorly controlled asthma need to be re-evaluated. Acta Paediatr (Oslo, Norway : 1992). 2015;104(5):e206–9.
81. Knutsen AP, Noyes B, Warrier MR, Consolino J. Allergic bronchopulmonary aspergillosis in a patient with cystic fibrosis: diagnostic criteria when the IgE level is less than 500 IU/mL. Ann Allergy Asthma Immunol. 2005;95(5):488–93.
82. Slavin RG, Bedrossian CW, Hutcheson PS, Pittman S, Salinas-Madrigal L, Tsai CC, et al. A pathologic study of allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol. 1988;81(4):718–25.
83. Vicencio AG, Santiago MT, Tsirilakis K, Stone A, Worgall S, Foley EA, et al. Fungal sensitization in childhood persistent asthma is associated with disease severity. Pediatr Pulmonol. 2014;49(1):8–14.
84. Boch T, Reinwald M, Spiess B, Liebregts T, Schellongowski P, Meybohm P, et al. Detection of invasive pulmonary aspergillosis in critically ill patients by combined use of conventional culture, galactomannan, 1-3-beta-D-glucan and Aspergillus specific nested polymerase chain reaction in a prospective pilot study. J Crit Care. 2018;47:198–203.
85. Kono Y, Tsushima K, Yamaguchi K, Kurita N, Soeda S, Fujiwara A, et al. The utility of galactomannan antigen in the bronchial washing and serum for diagnosing pulmonary aspergillosis. Respir Med. 2013;107(7):1094–100.
86. Farrant J, Brice H, Fowler S, Niven R. Fungal sensitisation in severe asthma is associated with the identification of Aspergillus fumigatus in sputum. J Asthma. 2016;53(7):732–5.
87. Agarwal R, Aggarwal AN, Gupta N, Gupta D. A rare cause of acute respiratory failure–allergic bronchopulmonary aspergillosis. Mycoses. 2011;54(4):e223–7.
88. Khalil KF. Therapeutic bronchoalveolar lavage with conventional treatment in allergic bronchopulmonary aspergillosis. J College Phys Surg Pakistan : JCPSP. 2015;25(5):359–62.
89. Licari A, Castagnoli R, Brambilla I, Marseglia A, Tosca MA, Marseglia GL, et al. Asthma Endotyping and biomarkers in childhood asthma. Pediatr Allergy Immunol Pulmonol. 2018;31(2):44–55.
90. Fitzpatrick AM, Moore WC. Severe asthma phenotypes – how should they guide evaluation and treatment? J Allergy Clin Immunol Pract. 2017;5(4):901–8.
91. Good JT Jr, Kolakowski CA, Groshong SD, Murphy JR, Martin RJ. Refractory asthma: importance of bronchoscopy to identify phenotypes and direct therapy. Chest. 2012;141(3):599–606.
92. de Blic J, Tillie-Leblond I, Tonnel AB, Jaubert F, Scheinmann P, Gosset P. Difficult asthma in children: an analysis of airway inflammation. J Allergy Clin Immunol. 2004;113(1):94–100.
93. Tortajada-Girbes M, Bousquet R, Bosque M, Carrera Martinez JJ, Ibanez MD, Moreira A, et al. Efficacy and effectiveness of omalizumab in the treatment of childhood asthma. Expert Rev Respir Med. 2018;12(9):745–54.
94. Amat F, Labbe A. Biomarkers for severe allergic asthma in children: could they be useful to guide disease control and use of omalizumab? Expert Rev Respir Med. 2018;12(6):475–82.
95. Kuprys-Lipinska I, Molinska K, Kuna P. The effect of omalizumab on eosinophilic inflammation of the respiratory tract in patients with allergic asthma. Pneumonol Alergol Pol. 2016;84(4):232–43.
96. Deeks ED. Mepolizumab: a review in eosinophilic asthma. BioDrugs. 2016;30(4):361–70.

97. Kelly EA, Esnault S, Liu LY, Evans MD, Johansson MW, Mathur S, et al. Mepolizumab attenuates airway eosinophil numbers, but not their functional phenotype, in asthma. Am J Respir Crit Care Med. 2017;196(11):1385–95.
98. Keating GM. Mepolizumab: first global approval. Drugs. 2015;75(18):2163–9.
99. Al Efraij K, FitzGerald JM. Benralizumab for the add-on maintenance treatment of patients with severe asthma aged 12 years and older with an eosinophilic phenotype. Expert Rev Clin Pharmacol. 2018;11(7):669–76.
100. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet (London, England). 2016;388(10056):2115–27.
101. Erkman J, Segal L, Levine J, Moy L, Greifer M, Giusti R, et al. Association of Airway Esophageal Eosinophils in children with refractory asthma and chronic cough. Chest. 2017;152(4):A845.
102. Chetta A, Zanini A, Foresi A, Del Donno M, Castagnaro A, D'Ippolito R, et al. Vascular component of airway remodeling in asthma is reduced by high dose of fluticasone. Am J Respir Crit Care Med. 2003;167(5):751–7.
103. Hoshino M, Takahashi M, Takai Y, Sim J, Aoike N. Inhaled corticosteroids decrease vascularity of the bronchial mucosa in patients with asthma. Clin Exp Allergy. 2001;31(5):722–30.
104. Sont JK, Willems LN, Bel EH, van Krieken JH, Vandenbroucke JP, Sterk PJ. Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. Am J Respir Crit Care Med. 1999;159(4 Pt 1): 1043–51.
105. Ward C, Pais M, Bish R, Reid D, Feltis B, Johns D, et al. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. Thorax. 2002;57(4):309–16.
106. Breborowicz A, Niedziela M. Adrenal function in children with severe asthma treated with high-dose inhaled glucocorticoids: recommended screening tests in outpatient conditions. J Pediatr Endocrinol Metab. 2007;20(7):781–9.
107. Kang JY, Jo MR, Kang HH, Kim SK, Kim MS, Kim YH, et al. Long-term azithromycin ameliorates not only airway inflammation but also remodeling in a murine model of chronic asthma. Pulm Pharmacol Ther. 2016;36:37–45.
108. Liu Y, Pu Y, Li D, Zhou L, Wan L. Azithromycin ameliorates airway remodeling via inhibiting airway epithelium apoptosis. Life Sci. 2017;170:1–8.
109. Zhao X, Yu FQ, Huang XJ, Xu BY, Li YL, Zhao XY, et al. Azithromycin influences airway remodeling in asthma via the PI3K/Akt/MTOR/HIF-1alpha/VEGF pathway. J Biol Regul Homeost Agents. 2018;32(5):1079–88.
110. Kelly C, Chalmers JD, Crossingham I, Relph N, Felix LM, Evans DJ, et al. Macrolide antibiotics for bronchiectasis. Cochrane Database Syst Rev. 2018;3:CD012406.
111. Mayer-Hamblett N, Retsch-Bogart G, Kloster M, Accurso F, Rosenfeld M, Albers G, et al. Azithromycin for Early Pseudomonas Infection in Cystic Fibrosis: The Optimize Randomized Trial. American journal of respiratory and critical care medicine. 2018;198(9):1177–87
112. Hilliard TN, Regamey N, Shute JK, Nicholson AG, Alton EW, Bush A, et al. Airway remodelling in children with cystic fibrosis. Thorax. 2007;62(12):1074–80.
113. Turato G, Barbato A, Baraldo S, Zanin ME, Bazzan E, Lokar-Oliani K, et al. Nonatopic children with multitrigger wheezing have airway pathology comparable to atopic asthma. Am J Respir Crit Care Med. 2008;178(5):476–82.
114. Reiter J, Demirel N, Mendy A, Gasana J, Vieira ER, Colin AA, et al. Macrolides for the long-term management of asthma--a meta-analysis of randomized clinical trials. Allergy. 2013;68(8):1040–9.
115. Gibson PG, Yang IA, Upham JW, Reynolds PN, Hodge S, James AL, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet (London, England). 2017;390(10095):659–68.
116. Webley WC, Hahn DL. Infection-mediated asthma: etiology, mechanisms and treatment options, with focus on Chlamydia pneumoniae and macrolides. Respir Res. 2017;18(1):98.
117. Slater M, Rivett DW, Williams L, Martin M, Harrison T, Sayers I, et al. The impact of azithromycin therapy on the airway microbiota in asthma. Thorax. 2014;69(7):673–4.
118. Piacentini GL, Peroni DG, Bodini A, Pigozzi R, Costella S, Loiacono A, et al. Azithromycin reduces bronchial hyperresponsiveness and neutrophilic airway inflammation in asthmatic children: a preliminary report. Allergy Asthma Proc. 2007;28(2):194–8.
119. Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, et al. Long-term azithromycin for indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (bronchiectasis intervention study): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med. 2013;1(8):610–20.
120. Karbasi A, Ardestani ME, Ghanei M, Harandi AA. The association between reflux esophagitis and airway hyper-reactivity in patients with gastro-esophageal reflux. J Res Med Sci. 2013;18(6):473–6.
121. Coughlan JL, Gibson PG, Henry RL. Medical treatment for reflux oesophagitis does not consistently improve asthma control: a systematic review. Thorax. 2001;56(3):198–204.

122. Nakase H, Itani T, Mimura J, Kawasaki T, Komori H, Tomioka H, et al. Relationship between asthma and gastro-oesophageal reflux: significance of endoscopic grade of reflux oesophagitis in adult asthmatics. J Gastroenterol Hepatol. 1999;14(7):715–22.
123. Hill CA, Ramakrishna J, Fracchia MS, Sternberg D, Ojha S, Infusino S, et al. Prevalence of eosinophilic esophagitis in children with refractory aerodigestive symptoms. JAMA Otolaryngol Head Neck Surg. 2013;139(9):903–6.
124. Kia L, Hirano I. Distinguishing GERD from eosinophilic oesophagitis: concepts and controversies. Nat Rev Gastroenterol Hepatol. 2015;12(7):379–86.
125. Gutierrez-Junquera C, Fernandez-Fernandez S, Cilleruelo ML, Rayo A, Echeverria L, Quevedo S, et al. High prevalence of response to proton-pump inhibitor treatment in children with esophageal eosinophilia. J Pediatr Gastroenterol Nutr. 2016;62(5):704–10.
126. Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? Clin Gastroenterol Hepatol. 2004;2(7):523–30.
127. Yakoot M. Eosinophilic digestive disease (EDD) and allergic bronchial asthma; two diseases or expression of one disease in two systems? Ital J Pediatr. 2011;37:18.
128. Assa'ad AH, Gupta SK, Collins MH, Thomson M, Heath AT, Smith DA, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology. 2011;141(5):1593–604.
129. Kuang FL, Alao H, Kumar S, Powers A, Quezado M, Wang Z. Benralizumab (anti-IL5Ra) depletes gut tissue eosinophilia and improves symptoms in hypereosionphilic syndrome with gastrointestinal involvement. J Allergy Clin Immunol. 2018;141:AB196.

Foreign Body Aspiration: The Role of the Pediatric Pulmonologist

25

Pelton A. Phinizy

Introduction

Foreign body aspiration is a major medical problem affecting primarily children and the elderly. It can be a life-threatening emergency and, at times, a diagnostic dilemma. The role the pediatric pulmonologists play is multifaceted and collaborative. At the initial presentation, the pulmonologist can assist the frontline clinicians in the clinic, urgent care, or emergency department setting with the diagnostic evaluation using physical exam, radiographic examination, and possibly confirmatory flexible bronchoscopy. Then once the foreign body is found, rigid bronchoscopy is usually the safest method for extraction; however, the pulmonologist can take on an interventional role instead of just one as a diagnostician and help with the removal of foreign bodies. This role is particularly salient when the foreign body is located in a distal airway or the size and shape of the foreign body makes it more amenable to extraction utilizing some of the tools that the flexible bronchoscopist has at their disposal. Following removal, the pulmonologist is vital in helping with post-operative management including the identification and treatment of complications both acutely and chronically.

Epidemiology

Most of the time, the pulmonologist will not be the first medical provider to see the patient in question. In order to help frontline clinicians with diagnosis or to make the diagnosis oneself, it is important to understand the problem one is facing from an epidemiologic standpoint.

Foreign body aspiration is a common medical emergency in pediatrics. Exact incidence and prevalence may be underestimated because of choking episodes that are relatively transient or treated at home that we do not have a way of accounting for. Many events do not result in a visit to the doctor's office or emergency room. But there are more serious events which do result in a visit to a health professional: according to the Center for Disease Control, foreign body aspiration was associated with over 17,000 emergency room visits in the United States in 2001 [1]. A more recent study using the Nationwide Inpatient Sample over a 3-year period from 2009 to 2011 in the United States found that about 1900 patients were admitted to hospitals with bronchial foreign body aspiration. Of that group about 2% suffered anoxic brain injury and almost 2% died [2]. More

Electronic Supplementary Material: The online version of this chapter (https://doi.org/10.1007/978-3-030-54924-4_25) contains supplementary material, which is available to authorized users.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_25

than the loss of lives, there is also the economic burden of foreign body aspiration. One study estimated the annual cost to be approximately $41 million in inpatient healthcare expenditures in the United States [2].

There are two peaks in prevalence for foreign body aspiration, and they tend to occur in the pediatric age group and the geriatric age group. Young children and children with developmental or neurologic impairments are especially at risk. According to one large sample, about 90% of patients with foreign body aspiration were less than 3 years of age with the peak prevalence between 1 and 2 years of age [3]. Similar findings are found in other large samples [4–6]. It is thought to occur more frequently in children because of their behavioral and developmental characteristics. Young children have more immature swallowing and coughing mechanisms, they will explore their environment by placing objects into their mouths, and they will walk, run, play, jump, and talk with food or foreign bodies in their mouth—literally a recipe for trouble. In older children and adolescents, alcohol and sedating medications contribute to increased risk.

Not only do the youngest children have the highest incidence of foreign body aspiration but they are also the most vulnerable population. A large national sample of mortality due to food-related asphyxiation in children found that 90% had occurred in children younger than 5 years and 65% in infants younger than 2 years [7]. Similarly, reports of mortality from the United States Consumer Product Safety Commission, which records data on non-food items, found that 65% of deaths were children aged less than 3 years [8]. The small size of the airways puts younger children at greater risk for significant impairment with even relatively small foreign bodies. Reductions in the cross-sectional area of the already diminutive airway can create significant obstruction as resistance to airflow is inversely proportional to the radius of the airway lumen to the fourth power. Essentially, a little obstruction can result in a great deal of resistance and this is especially true in younger children. In the youngest children, all foreign body aspirations, no matter the size, need to be considered life-threatening.

What kinds of objects are being aspirated? Foods are common but so are non-food items. Children in the first 2 years of life are more likely to aspirate food, whereas older children are more likely to aspirate non-food items such as pen caps, pins, and paper clips. Among all age groups, commonly aspirated foods include nuts, seeds, legumes, grapes, carrots, apples, popcorn, hot dogs, and chicken. Non-food foreign bodies tend to be pins, nails, tacks, screws, pen tops, beads, and coins [7–10]. Not surprisingly, there is a cultural twist to these data, whereby certain objects may be more likely in certain countries. A large case study from Egypt, for example, found that scarf pins, a common women's accessory in the country, were among the most frequently aspirated foreign bodies [11].

Certain foods and objects are considered more high risk for significant obstruction or death based on their size, shape, and composition. Foods associated with the highest risk in children are round or cylindrical, roughly the size of a pediatric airway, and somewhat compressible such that they are able to wedge thoroughly into the airway. These include many foods that are, at least in the United States, traditionally popular with children such as hot dogs, whole grapes, seeds, nuts, raw carrots, hard candy, popcorn, marshmallows, chewing gum, and sausage [7]. Of particular concern are uninflated and broken pieces of latex balloons which result in about 7–10 deaths a year in the United States. These objects are particularly deadly because of their ability to accommodate to the shape of the airway and form an airtight seal [12–14].

Two other notable foreign bodies are magnets and batteries. Both of these foreign bodies are more infamous for their role in foreign body ingestion and the potential morbidity associated with their presence in the gastrointestinal tract [15]. Magnets are dangerous because the force of attraction between two magnets can lead to tissue ischemia and subsequently gastrointestinal perforation if tissue or bowel is caught between the magnets. Ingested button batteries—especially those that become lodged in the esophagus and do not pass through to the stomach—can result in tremendous tissue damage in a relatively short amount of time.

As children will continue to behave like children, anything that can be accidentally swallowed can be accidentally aspirated. There is a case report of a 3-year-old girl who aspirated one magnet and ingested another such that they were attracted to each other and over the course of the 3 months that they remained in place, created a broncho-esophageal fistula [16]. In another case report, a 4-year-old boy aspirated a button battery. He developed mucosal inflammation, necrosis, and strictures initially, and at 4 months after removal, he had residual mild bronchial stenosis. While the airway injury in this case report was significant, it was not nearly as destructive as a button battery in the esophagus can be. It is unclear if this case represents a typical course for button battery aspiration, as there are so few in the reported literature [17].

When a foreign body is aspirated, it can be found virtually anywhere within the airway. Age of the patient, size of the airway, as well as the size of the foreign body, all play a role in where the foreign body will come to lie. The most likely location for a foreign body is in the mainstem bronchi but foreign bodies can be found more proximally in the larynx or trachea or more distally in the subsegmental bronchi [18]. There is some variability in the literature, but it appears that foreign bodies have a slight preference for the right side of the bronchial tree if they are going to settle below the carina [4, 19–21]. Different studies also quote different morbidity and mortality based on location with some stating that more proximal foreign bodies, for example, those located in the larynx, are generally associated with more mortality and others stating that distally located foreign bodies are associated with more mortality [18, 22, 23]. This variability in the literature is likely due to the wide range of different foreign bodies with diverse sizes, shapes, and impacts on the airway mucosa. No matter the location, it is important to have a healthy amount of respect for any foreign body in the airway.

Presentation

Symptoms and severity may vary greatly depending on the foreign body that has been aspirated. The size and shape of the object, where it is located in the airway, and the amount of time that has passed from the initial aspiration all may impact the signs and symptoms. A cyanotic child with altered mental status and/or severe respiratory distress is an example of complete or near complete obstruction of the airway and is a medical emergency requiring immediate intervention. The more common presentation is a partial obstruction of the airway associated with milder symptoms. The latter patients can afford to undergo a more detailed history and physical exam. The most common symptom is typically acute onset of cough but other signs and symptoms that can be seen include tachypnea, dyspnea, stridor, wheeze, hemoptysis, hoarse voice, fever, and chest or throat pain [4, 24].

The classic physical examination findings for a foreign body aspiration are those of a patient with wheeze, cough, and diminished breath sounds. However, as was seen in 61% of a large retrospective study, many patients will not have all three of these "classic" findings [25]. Physical examination findings suggestive of foreign body aspiration may include wheeze, stridor, rales, localized or unilaterally diminished breath sounds, tachypnea, and respiratory distress [10, 26]. In one large study, 7% of patients had no finding on physical exam to suggest an aspirated foreign body [25]. Given the large variety of possible foreign bodies and the diverse locations within the airway that they may settle, it is not surprising that there is heterogeneity of the signs and symptoms.

The physical exam may be able to indicate where the foreign body has come to rest. Obstruction can result in adventitial lung sounds or noisy breathing because it makes the airflow more turbulent. In general, obstruction above the level of the thoracic inlet tends to cause a high-pitched inspiratory wheeze (frequently called stridor), obstruction that is below the level of the thoracic inlet tends to cause a high-pitched expiratory wheeze, and obstruction at or close to the level of the thoracic inlet tends to cause biphasic wheeze. A foreign body that has settled on one side or the other of the bronchial tree may result in unilateral wheeze and/or diminished breath sounds.

History of a choking event should certainly increase one's suspicion for an aspirated foreign body. In one prospective study, choking followed by a paroxysmal episode of coughing was the most common presentation for foreign body aspiration and the sensitivity and specificity of finding an aspirated foreign body for this combination was 91% and 45.2%, respectively [26]. The initial choking event can be followed by an inappropriately reassuring asymptomatic period which may lead to a delayed diagnosis [9]. Occasionally, there is no history of a choking event preceding the development of symptoms [25]. Children may have choking events that are not witnessed or events that the family does not think are relevant until directly questioned about it. From personal experience, a family thought that the referring physician had communicated the history and so the family did not specifically discuss the choking incident during the clinic visit. Only after a month of medical treatments, in which the patient saw no improvement, was the family asked if there might have been a choking event. Subsequently, the granola that the young boy had choked on while jumping on a trampoline was removed from the airway without incident and his chronic cough resolved. It is important to keep foreign body aspiration in mind even when no specific history of choking is imparted and just as important to ask about it clearly and explicitly.

Because there may not be a witnessed event, and there may be an asymptomatic period, the length of time elapsed from the aspiration event may vary. Delays in diagnosis can lead to complications such as atelectasis, pneumothorax, pneumomediastinum, persistent or recurrent pneumonia, pulmonary abscess, bronchiectasis, tracheoesophageal fistula, or bronchoesophageal fistula [27, 28]. Delays in diagnosis of even 24 hours may help accentuate pathologic findings on physical exam, chest radiograph, and fluoroscopy but in the absence of a witnessed choking event does not necessarily make establishing the diagnosis of foreign body aspiration any easier [25, 26].

Evaluation

Following a detailed history and physical exam, if a foreign body aspiration is suspected further evaluation can be performed. Chest radiography is often the first method employed and can readily identify radiopaque objects. While radiolucent foreign bodies may not be easily identified on chest radiograph, one may be able to detect secondary signs that are the result of a foreign body. The most common secondary sign is that of air trapping or obstructive emphysema due to ball-valve effect blocking exhalation from the bronchus by the foreign body (See Fig. 25.1). Comparing inspiratory and forced expiratory films can help identify this sign but may be dif-

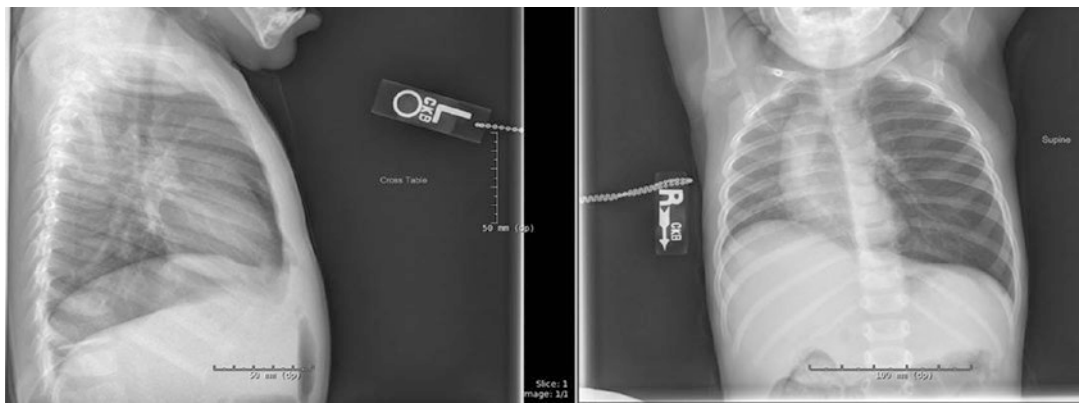

Fig. 25.1 Cross-table and supine chest radiographs demonstrating left lung hyperinflation and mediastinal shift in a patient with a foreign body in the left mainstem bronchus

ficult to obtain in some children, particularly the youngest age group who are at the highest risk of aspiration. In children who are not able to participate with this maneuver, lateral decubitus films may reveal relative obstructive emphysema of the impacted lung when it is in the dependent position. Another option to detect this unilateral emphysema is airway fluoroscopy performed with the child breathing deeply. The downside of this approach is a relatively larger dose of radiation. Other findings associated with foreign body on chest radiography include atelectasis, pneumonia, pneumothorax, and pneumomediastinum [29].

Computed tomography of the chest is another option. It has excellent sensitivity in retrospective studies, 100% in three smaller published series. It also has very good specificity—between 66.7% and 100% in the same three series. The false positives in these studies were due to mucus plugs and artifact. While technology for computed tomography has been improving and a scan of the chest can be performed fairly quickly, the downside of this approach is again that it requires either a cooperative patient or sedation and it is associated with more radiation than plain radiographs [29]. However, it is being considered an alternative to the gold standard, flexible bronchoscopy.

Flexible bronchoscopy, in the hands of a trained bronchoscopist, allows one to visualize the airways to confirm or refute the presence of an airway foreign body. In children, the airways are typically so small that almost any clinically significant foreign body would be found in the visible range of the flexible bronchoscope, for example, the first 3–5 generations of the airways. However, in adolescents and adults, smaller foreign bodies may lodge themselves more distally, potentially beyond the areas that are easiest to visualize. Other circumstances may make it more difficult to visualize a foreign body even with flexible bronchoscopy. Factors that might make it more difficult to identify a foreign body include blood in the airway, a strong inflammatory reaction that results in increased airway secretions and granulation tissue formation (e.g., With a peanut foreign body), or the concomitant presence of pneumonia or post-obstructive pneumonia. Even with some of these factors that may make it more difficult to potentially identify a foreign body, direct visualization via flexible bronchoscopy is still considered the gold standard given its maneuverability within the airways.

Rigid bronchoscopy is useful to survey the airways for a foreign body in circumstances when the physical exam or imaging imply that the foreign body may have settled in the central airway or main stem bronchi or the foreign body is thought to be too large to have settled more distally. This is because the rigid bronchoscope can visualize these areas well and then be in a position to remove the foreign body.

A potential drawback of either rigid or flexible bronchoscopy for diagnostic evaluation is that the patient will require anesthesia. There is sometimes concern with the application of medications that will further inhibit airway protective mechanisms such as coughing. However, once under anesthesia, if a foreign body is identified, flexible or rigid bronchoscopy can then be used to facilitate the removal of the identified foreign body. Bronchoscopy thus can serve both as a more exhaustive diagnostic technique and as a definitive treatment in most cases. While the potential risks of an anesthetic need to be considered, these procedures are safe and very well tolerated in well-trained hands [30]. And even if a foreign body is not identified, alternative diagnoses may be found or one can provide peace of mind to patient, parents, and other providers that there is not an aspirated foreign body. In general, given the low risk of performing a flexible bronchoscopy procedure, it may be advisable to rule out a foreign body rather than run the risk of developing complications from a delay in definitive diagnosis and treatment.

Each case is different but I generally let the history, physical exam, and initial diagnostic testing guide much of my decision-making. If imaging confirms the presence of a foreign body or is highly suspicious for the presence of a foreign body, the next step should be rigid bronchoscopy to confirm and subsequently remove it. If there is history, physical exam findings, or diagnostic testing that

would put foreign body on the differential among other diagnoses then flexible bronchoscopy can be considered as an alternative to rigid bronchoscopy for diagnostic confirmation. The specific circumstances might push a provider toward one or the other to help with ruling out or in the other potential diagnoses on the differential. For example, if there is stridor, suggesting a more proximal, extrathoracic foreign body, rigid bronchoscopy might be preferred. But if there is unilateral expiratory wheeze, suggesting a more distal foreign body, flexible bronchoscopy might be preferred. Other cases might call for having providers capable of performing both rigid and flexible bronchoscopy in the operating room together to assist each other. Whenever I am performing a flexible bronchoscopy and feel that the presence of a foreign body is high enough on the differential, it is my practice to ensure that there is an otolaryngologist comfortable with foreign body removal present in the operating room and setup to perform rigid bronchoscopy at the time of the flexible bronchoscopy.

Treatment: Foreign Body Retrieval

History of Foreign Body Retrieval

Historically, foreign body aspiration was associated with grim outcomes. It was considered a "miracle" to survive as there was virtually no way to remove the offending foreign body. St. Blaise, originally a physician and later a bishop, became patron saint of throat ailments with the miraculous act of saving a young boy who was choking on a fish bone.

In the eighteenth and nineteenth centuries, the grim prognosis was literally flipped on its head as endoscopy replaced prayer. Chevalier Jackson, a pioneering laryngologist, is credited with helping to reduce the mortality associated with foreign body aspiration from 98% to around 2%—where it continues to stand today. He achieved this by developing some of the first rigid bronchoscopes and improving many endoscopic techniques for foreign body retrieval. As a dedicated and hard-working physician, he was also famous for collecting and archiving the over 2000 objects he removed. His impressive collection of foreign bodies is on display today at the Mütter Museum in Philadelphia, Pennsylvania [31].

Another major milestone in the treatment of foreign bodies was the development of the flexible bronchoscope by Shigeto Ikeda in 1962 and over the next 20 years, the introduction of and then expansion of its use in the pediatric population by Robert Wood and other pulmonologists. Initially developed primarily as a diagnostic tool, it has found therapeutic uses as well [32–35].

Modern Methods of Foreign Body Retrieval

Conventional first-line treatment for aspirated foreign bodies is rigid bronchoscopy and in many pediatric academic centers, this is performed by otolaryngologists or general pediatric surgeons. Rigid bronchoscopy allows for control of the airway facilitating effective gas exchange while simultaneously enabling more secure manipulation of the airways and of foreign bodies with various tools and instruments under direct visualization. The ability to remove a foreign body while maintaining sight of it and having continuous control of the airway is one that should not be undervalued. A potentially fatal complication of foreign body retrieval is to lose grip of the foreign body as it is being extracted from the airway—typically at the level of the larynx, cricoid, or trachea—resulting in central airway obstruction. With direct visualization and maintenance of a stable airway this potentially very serious complication can typically be corrected rather quickly. Another advantage of the rigid bronchoscope is that there is generally better visual clarity and brightness, although with the latest flexible bronchoscopes this is becoming less of an issue. A number of different forceps have been developed for use with the rigid bronchoscope to help manipulate a variety of objects. Suction can also be introduced alongside which is especially useful in instances when there is significant bleeding, pus, or granulation tissue obstructing the view. The disadvantages of rigid bronchoscopy are that there is sometimes limited access to or

ability to visualize the more distal airways beyond the trachea and the mainstem bronchi and rigid bronchoscopy can result in varying degrees of trauma to the airway. It is also not considered safe to perform rigid bronchoscopy on a patient with an unstable cervical spine.

While flexible bronchoscopy is an excellent method for diagnosing a foreign body aspiration (especially an occult one), rigid bronchoscopy remains the standard of care for retrieval of foreign bodies. However, over the last few decades, using flexible bronchoscopy alone or in conjunction with rigid bronchoscopy to remove a foreign body is gaining in popularity. This is likely due to the increasing availability of flexible bronchoscopes that are smaller in size, but have improved visual clarity and still maintain working channels sufficient for the instruments needed to help remove a foreign body. In fact, a number of studies have shown flexible bronchoscopy to be both safe and effective for the removal of foreign bodies in pediatric and adult patients [36–42]. Others have found that it appears to take a shorter amount of time to perform flexible bronchoscopy compared with rigid bronchoscopy and that flexible bronchoscopy was able to remove foreign bodies located too distal in the airways for the rigid bronchoscope [42]. But, there are no well-designed randomized trials pitting the two methods head-to-head to compare efficacy and safety. It is not clear that this would be feasible with the very low rate of significant complications for both. This author generally recommends the rigid bronchoscopic approach for foreign body retrieval, but there are situations when the flexible fiberoptic bronchoscope, and those that are comfortable wielding it, may have an advantage over the rigid bronchoscope. The three main instances when a flexible bronchoscope should be used are as follows:

- The foreign body has settled in a distal airway or in a lobe that is difficult for the rigid bronchoscopist to reach.
- There are small fragments of foreign body and one wants to confirm complete removal.
- The characteristics of the foreign body make it more amenable to removal with the instruments available to the flexible bronchoscopist.

The major strength of the flexible fiberoptic bronchoscope is that it is smaller and more flexible than the rigid bronchoscope and can maneuver more freely throughout the tracheobronchial tree. One is generally able to interrogate the upper lobes as well as more distal airways more easily than with the rigid bronchoscope. This freedom allows for a more complete evaluation of the subsegmental bronchi when evaluating for presence or absence of a foreign body but also permits greater access to a foreign body located more distally. This may also be useful in patients with smaller size of their airways or abnormal anatomy that make rigid bronchoscopy more difficult [43, 44].

It is especially important to be able to investigate smaller or more distal airways when there is a foreign body that has broken up and/or spread out throughout the airway. This can be seen with food which may have been masticated prior to aspirating. It may also be seen with nuts or brittle foreign bodies that break into smaller pieces iatrogenically when grabbed by forceps. It is extremely helpful for the flexible bronchoscopist to be able to systematically visualize the more distal airways and identify persistent retained foreign bodies or confirm complete retrieval after the primary retrieval has been completed.

Lastly, the characteristics of the foreign body may make it more amenable to a specific approach. The size, shape, and material composition of the foreign body, as well as where it has settled in the airway should all be considered when planning a retrieval. Having a working knowledge of the instruments available to you as well as the imagination and creativity to apply them will benefit the bronchoscopist.

The major downside of flexible bronchoscopy as a method for foreign body retrieval is that the bronchoscope and the foreign body typically need to be removed simultaneously. This means that one loses visualization of the airway for a period of time. If the foreign body is too large to be removed through the inner lumen of the endotracheal tube or the laryngeal mask airway, the advanced airway may need to be removed simultaneously and that means losing both visualization and control of the airway. This is a dangerous

situation and one that the entire care team should be prepared for, as the patient may need to have an advanced airway replaced quickly. It is also possible when withdrawing the scope to drop the foreign body in a position to obstruct the central airway. If this happens when the flexible bronchoscope and the artificial airway are being removed, it could have significant consequences. The team approach, good communication, and preparedness are absolutely necessary. Possible problems and how to react to them should be discussed with the team prior to performing more difficult or risky maneuvers. The team should be prepared with replacement airways and the anesthesia team ready to deploy them.

Another option that helps overcome some of the shortcomings of both techniques is to use a combined approach wherein the flexible bronchoscope brings the foreign body within range of the rigid bronchoscope and the rigid bronchoscopist then removes the foreign body while maintaining visualization, a stable airway, and often times a better grip on the foreign body. Some centers that do not have access to rigid bronchoscopes have published their alternative methods. They will perform a temporary tracheostomy at the time of retrieval to aid with the removal of the foreign body via the newly created stoma after it is brought to the central airway by the flexible bronchoscope [45, 46].

Anesthetic Considerations for Retrieval with a Flexible Bronchoscope

When performing extraction with a flexible bronchoscope, it is always important to consider all the aspects of the case including anesthetic choices. Choice of inhaled versus intravenous induction, artificial airway versus natural airway, and spontaneous versus controlled ventilation should be determined prior to the procedure with emergency plans made if problems arise along the way. There is no consensus in the literature as to which methods are best and given the heterogeneity of foreign bodies and techniques for removal, it is best to plan for the case in front of you instead of following a specific protocol. Thinking ahead and being prepared can lead to better outcomes. It should also be emphasized that teamwork and communication are always important in the operating room but perhaps more so during cases of foreign body retrieval as the risk of sudden decompensation is great.

When the patient is in extremis or is at risk of central airway obstruction, they should be taken to the operating room emergently. Aspiration of stomach contents may be avoided by suctioning the stomach prior to bronchoscopy for emergent cases. However, an anesthetic fast may be appropriate for stable patients with a lower risk for deterioration due to central airway obstruction.

Induction that allows for spontaneous breathing is favored in the literature because of the risk of converting a partial obstruction to a complete obstruction when the patient's own spontaneous negative pressure ventilation is converted to a controlled positive pressure ventilation [47]. An anesthetic gas may be useful for induction to help with maintenance of spontaneous breathing, but during the procedure, there are several sources of leak in the circuit and ventilation may be compromised with either a rigid or flexible bronchoscope in the airway. Therefore, maintenance of anesthesia using an intravenous medication may be preferable as it can provide continuous anesthesia [37].

Having an idea of what was aspirated and how large it is may help determine whether to use a laryngeal mask airway or an endotracheal tube, although this may not be known prior to the procedure and the size may have changed, as some objects will swell with moisture in the airways. A laryngeal mask airway may be preferred because the larger internal lumen allows for extraction of larger foreign bodies; however, this can leave the patient vulnerable to laryngospasm which an endotracheal tube would prevent. With either of these artificial airways, it may be necessary to change or replace them during the case in the event of obstruction or needing to remove the foreign body, flexible bronchoscope, and artificial airway *en bloc*. For these reasons, it may be advisable to use only a thoughtfully measured amount of tape to secure the airway and to have

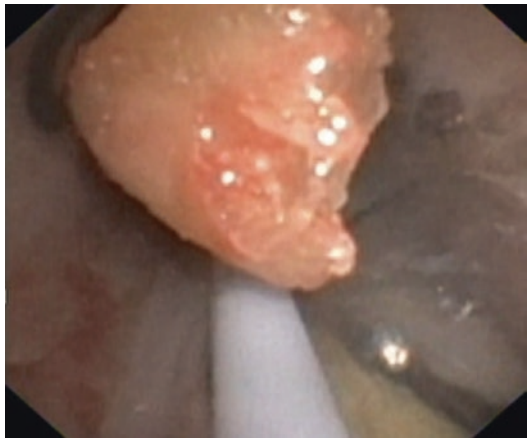

Fig. 25.2 Fragment of a peanut that became lodged in an endotracheal tube upon retrieval

backup airways immediately available as one may need to replace an artificial airway hastily. See Fig. 25.2 for an example of an endotracheal tube that became obstructed with a chunk of peanut as it was being retrieved. If, based on patient size, flexible bronchoscope size, and expected size of the foreign body, neither the laryngeal mask airway nor endotracheal tube is suitable, one may opt to introduce the flexible bronchoscope orally while the anesthesiologist maintains spontaneous breathing and passive oxygenation. In lieu of spontaneous ventilation, for the patient who may not tolerate spontaneous ventilation, intermittent periods of controlled ventilation via endotracheal tube followed by and alternating with extubation and brief periods of rapid bronchoscopic evaluation and foreign body retrieval have been implemented successfully [43].

Timing of Treatment

When determining the timing for bronchoscopic evaluation of the airways for foreign body or for removal of a foreign body a number of factors will need to be considered. Obviously, for the patient in extremis—one who has a complete airway obstruction—intervention needs to be undertaken immediately as asphyxiation can occur in minutes. As per the American Heart Association Basic Life Support guidelines, infants should receive back blows and chest compressions, while children 1 year of age and older should receive abdominal thrusts, also known as the Heimlich maneuver, to try to dislodge the foreign body [48].

If the foreign body cannot be expelled, intubation is an option for the patient with severe or complete airway obstruction to potentially provide some ventilation until more definitive treatment with rigid bronchoscopy is available. If there is complete or near complete obstruction of the central airway and it is not possible to immediately remove the obstruction, one may even be able to force the foreign body down one of the mainstem bronchi and then provide single lung ventilation. Another option for a more proximally located foreign body is to perform cricothyroidotomy to create a patent airway distal to an upper airway obstruction [45].

Outside of the immediately life-threatening scenario when action needs to be taken immediately, timing may depend on a number of factors. The availability of proficient staff, equipment, composition of the suspected foreign body, and patient factors should all be taken into account when determining when to treat. One center looked into the safety of waiting until the next morning for those patients who were not in severe respiratory distress and who had a suspected foreign body. They found no difference in adverse outcomes between the group treated immediately and the group delayed until normal business hours [49].

Flexible Bronchoscopy Techniques for Foreign Body Retrieval

If one understands the potential risks and benefits of using flexible bronchoscopy for foreign body retrieval, there are many methods by which one can use a flexible fiberoptic bronchoscope to remove a foreign body. The first is attaching the working channel to negative pressure and creating suction. The tip of the flexible bronchoscope can then be used to draw the foreign body out. It tends to work best on flexible or malleable objects that might partially lodge themselves in the suc-

tion channel or create a tight seal when suction is applied allowing for a good grip. Applying suction for several seconds before attempting to move the foreign body seems to improve adherence. Then, slow, measured movements can help to maintain that attachment. Suction by itself can help move many different objects, however, the drawback is that the grasp on the foreign object is less reliable and the object could be dropped in the central airway with potentially grave consequences.

Another method is to use biopsy forceps to grasp the foreign body (Fig. 25.3). There are a variety of biopsy forceps available and they generally do a similar job. It can be difficult to maneuver the forceps in smaller airways because when they are in the open position they may be wider than the airway. For this reason, one should refrain from opening the forceps until close to the foreign body. The goal is to use the forceps to grab hold of the foreign body and remove the foreign body, forceps, and flexible bronchoscope together. If the foreign body is larger than the inner diameter of the endotracheal tube or the opening in the laryngeal mask airway, the artificial airway may need to be removed simultaneously. When using the biopsy forceps, care needs to be taken with soft foreign bodies which may allow for bites to be taken out of them (Fig. 25.4) or brittle foreign bodies that may shatter preventing the bronchoscopist from easily grasping the entire foreign body. An alternative method is to use the biopsy forceps to "rake" or "sweep" out the foreign body by inserting them past the foreign body in the closed position and opening the forceps once past the foreign body. Potential complications of using forceps include bleeding and air leak.

Fig. 25.3 Biopsy forceps in the open position

Cystoscopy baskets can also be deployed via the working channel to envelop many different sizes and shapes of foreign body in the net-like structure of the device (Fig. 25.5). These baskets are typically used during cystoscopy for kidney or ureteral stone removal, but have found a place in the realm of foreign body removal. There are several varieties of baskets with different shapes and configurations but they generally accommodate nearly any shape of foreign body. In general, the procedure is to open the basket, maneuver it around the foreign body, and ensnare it by tightening the basket. The difficulty with using the

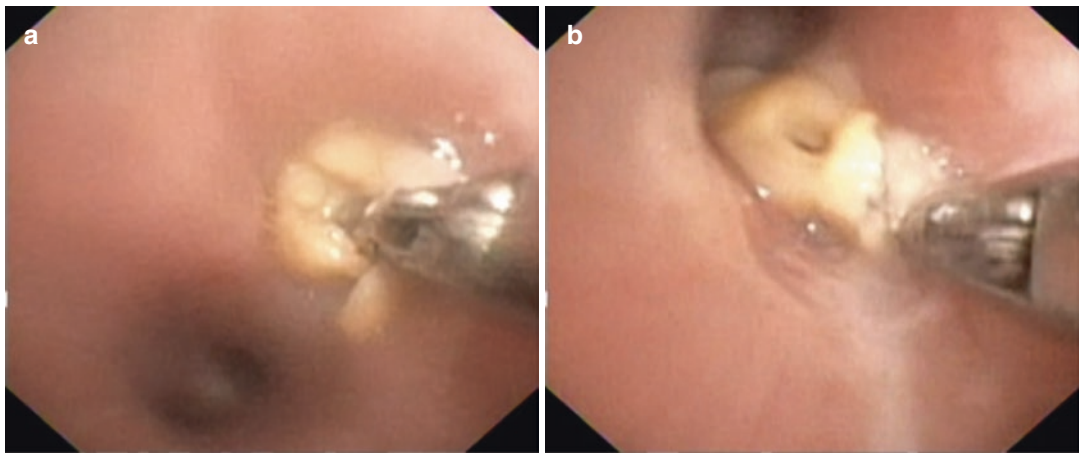

Fig. 25.4 Biopsy forceps (**a**) grasping a peanut foreign body and subsequently (**b**) "taking a bite out of the peanut" and pulling it apart, losing grip on the primary mass of the peanut

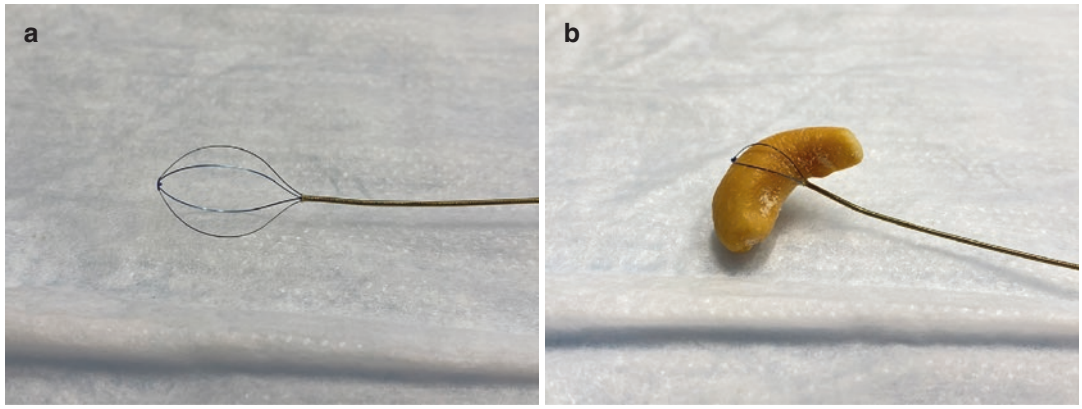

Fig. 25.5 Cystoscopy basket (**a**) in the open position and (**b**) ensnaring a peanut

cystoscopy basket is that one needs to be able to pass the distal portion of the basket beyond at least a portion of the foreign body in order to capture it in the net. If the foreign body is wedged in a subsegmental bronchus this may not be possible. It might be easiest to use suction or another modality to pull the foreign body proximally in order to give more room to maneuver the basket into a favorable position. The basket is probably one of the best ways to retrieve a smooth, rounded object that is otherwise difficult to get a grip on with forceps given that it surrounds the object or a portion of the object. It is also gentle enough that the more brittle foreign bodies like nuts will have a lower risk of shattering.

A cryotherapy probe is another option for foreign body retrieval in pediatrics (Fig. 25.6). However, it is limited by its size. It requires a working channel large enough to permit the 1.9 mm diameter cryotherapy probe. The cryotherapy probe functions by using liquefied gas, such as liquid nitrogen, that cools as it expands in the tip of the probe. The cold tip of the probe can be frozen to a foreign body in what is called "cryoadhesion" and then the foreign body, cryoprobe, and flexible bronchoscope can be removed from the airway. This method tends to work best with organic matter that has some water content although conversely will also work well with many metallic objects. Some bronchoscopists may spray the foreign body with saline to wet it and aid the freezing process. When freezing, one should ensure that the tip of the cryoprobe is touching only the foreign body and not the airway wall to prevent damage to the tissue. Generally, a shorter freezing cycle is used when performing cryoadhesion compared with a cryoablation procedure. This helps to ensure that only the foreign body freezes to the scope and that injury to the surrounding tissue is limited. Complications include edema, bleeding, and pneumothorax among others [50, 51].

If a foreign body has a hollow center such as a pen cap or bead, an endoscopic balloon or forceps may be able to be threaded through the opening, inflated, and then removed [52–55]. For a foreign object that doesn't already have a hole, lasers have been used to alter foreign bodies to make them easier to remove, in some cases by making or enlarging holes that balloons can be passed through [56]. The problems with using balloons are related to the possibility of fracturing the balloon and of potentially obstructing the airway with the balloon and foreign body.

Lastly, how does one retrieve a foreign body that is too distal to see? There is a case report of a teenage girl who aspirated a portion of a tongue ring into a subsegment of the right lower lobe. It could not be visualized under initial endoscopic surveillance, but this group used fluoroscopy to hone in on it. Then when they tried to use forceps to retrieve it, the forceps occluded their view of the foreign body. Again utilizing fluoroscopy, they were able to successfully retrieve the foreign body with the forceps [57].

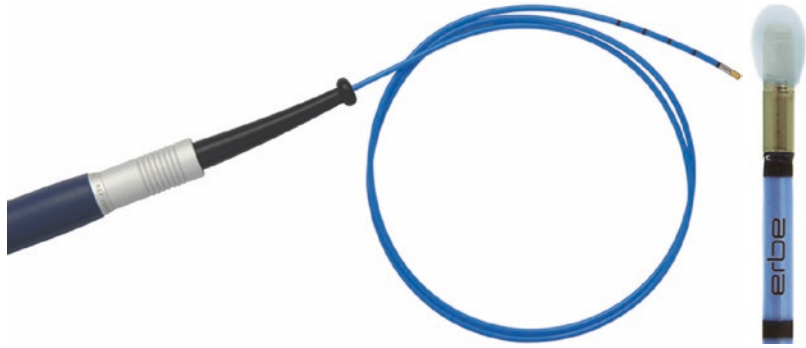

Fig. 25.6 The Erbokryo© Cryotherapy probe from ERBE

Ultimately, the aspect of a case of foreign body aspiration that makes it exciting is also what makes it daunting: no two cases are exactly the same, and there is a virtually endless supply of objects that could be aspirated. Therefore, the diagnosis of foreign body aspiration needs to always be considered and one needs to approach each case with an open mind about which method or methods should be employed to remove a foreign body and plans might need to be adjusted as the foreign body changes position within the airway as it is being worked on. In addition to dexterity with the flexible bronchoscope, creativity, imagination, and adaptability may need to be employed to get the best outcome for the patient.

Complications

Foreign bodies themselves have been associated with a number of complications. Acutely, the most immediately concerning complications are due to airway obstruction and how the foreign body affects normal gas exchange. A foreign body completely obstructing the airway can lead to hypoxemia and hypoventilation eventually resulting in death or hypoxemic ischemic injury if the obstruction is not relieved. Sharp or pointed foreign bodies can injure the tissue and result in bleeding or air leak such as pneumothorax or pneumomediastinum which may not be seen until the object is extracted. Organic material can absorb fluid from the surrounding airway and swell making it more obstructive and, potentially, more difficult to remove. A foreign body can also elicit inflammation and the development of granulation tissue in the airway. An example of a foreign body that causes significant inflammation and granulation tissue is a peanut. The tissue reaction is thought to be related to the oils [37]. In cases when there is too much inflammation, granulation tissue, or blood limiting the ability to visualize the foreign body, and the patient is otherwise stable, antibiotics and systemic corticosteroids can be used to help reduce inflammation over the subsequent 48–72 hours in order to return to the operating room when the procedure will be more likely to be successful. If the problem is simply mobilizing the foreign body and not visualizing the foreign body, others have instilled bronchial epinephrine to free the foreign body from the surrounding tissue [36].

If a foreign body or a fragment of a foreign body is unable to be removed or remains undiagnosed, there are three possible outcomes. The first is that perhaps it will travel up and out of the airways by way of mucociliary clearance and eventually be expectorated or swallowed. The second is that it will stay in the lung and not cause significant issue. The third is that it will remain in the lungs and can result in an inflammatory response and/or persistent obstruction resulting in recurrent or persistent infection. The most frequently mentioned complication is post-obstructive pneumonia, the result of the obstruction by the foreign body itself or of the edema, granulation, and stenosis secondary to the foreign body. Bronchiectasis is another not uncommon complication following prolonged foreign body aspiration. There is some evidence that it may be reversible following extraction of the foreign body. Other possibilities include air

leak such as pneumothorax or pneumomediastinum from damage to the tissue or even fistula formation such as tracheoesophageal fistula or bronchoesophageal fistula. It can also lead to what is sometimes called "destroyed lung" in the literature. This is lung parenchyma that is so irreversibly damaged by chronic or recurrent infections that lobectomy or pneumonectomy is generally recommended to reduce frequency of infections [58].

Complications associated with the procedural extraction of foreign bodies by flexible bronchoscope are relatively rare in well-trained hands but can be serious [59, 60]. As stated previously, this includes having the foreign body shift from a position of relative stability to one that obstructs the central airway. Severe laryngeal edema can occur following instrumentation. Bleeding can occur as a result of irritation or injury to the tissue by the foreign body itself or the instruments used. Minor bleeding typically resolves on its own. Moderate bleeding responds fairly well to tamponading with an endoscopic balloon, or bronchial instillation of ice-cold saline, ice-cold epinephrine, or oxymetazoline. More significant bleeding might require surgical intervention. Local swelling may occur and typically is well tolerated. For longer cases or when there is more significant swelling noted, systemic steroids may be employed to help with airway wall edema [37].

Follow-Up

Many patients that have a foreign body removed will have a very benign post-operative course. Some advocate that many can be discharged in less than 4 hours post-operatively or will have hospital stays of less than 1 day [4, 61]. Due to some of the complications of either the procedure or of the foreign body itself other patients may require longer hospital stays, bronchodilators, systemic corticosteroids, antibiotics, supplemental oxygen, or other respiratory support. After discharge, it is recommended to have the patient follow-up in the next few weeks specifically looking for symptoms of persistent foreign body or of complications from the procedure. If a patient remains symptomatic, it may even be necessary to repeat a bronchoscopy to ensure complete retrieval or to evaluate for any insidious complications.

Conclusion

The pulmonologist's role in foreign body aspiration is multifaceted. We serve as expert diagnosticians guiding evaluation and serve as ready participants in the ultimate treatment of the problem and of the potential complications. As far as treatment of a foreign body in the airway is concerned, rigid bronchoscopy remains the first-line treatment, but there is an expanding role for flexible bronchoscopy and the many tools in the flexible bronchoscopist's arsenal. Many in the literature think of flexible and rigid bronchoscopy in oppositional ways. I prefer to think that both have their strengths, and for many cases, it is likely best to work together to get the best outcomes for the patient.

References

1. Centers for Disease C, Prevention. Nonfatal choking-related episodes among children–United States, 2001. MMWR Morb Mortal Wkly Rep. 2002;51(42):945–8.
2. Kim IA, Shapiro N, Bhattacharyya N. The national cost burden of bronchial foreign body aspiration in children. Laryngoscope. 2015;125(5):1221–4.
3. Mu L, He P, Sun D. Inhalation of foreign bodies in Chinese children: a review of 400 cases. Laryngoscope. 1991;101(6 Pt 1):657–60.
4. Tan HK, Brown K, McGill T, Kenna MA, Lund DP, Healy GB. Airway foreign bodies (FB): a 10-year review. Int J Pediatr Otorhinolaryngol. 2000;56(2):91–9.
5. Schmidt H, Manegold BC. Foreign body aspiration in children. Surg Endosc. 2000;14(7):644–8.
6. Burton EM, Brick WG, Hall JD, Riggs W Jr, Houston CS. Tracheobronchial foreign body aspiration in children. South Med J. 1996;89(2):195–8.
7. Harris CS, Baker SP, Smith GA, Harris RM. Childhood asphyxiation by food. A national analysis and overview. JAMA. 1984;251(17):2231–5.
8. Rimell FL, Thome A Jr, Stool S, Reilly JS, Rider G, Stool D, et al. Characteristics of objects that cause choking in children. JAMA. 1995;274(22):1763–6.

9. Fitzpatrick PC, Guarisco JL. Pediatric airway foreign bodies. J La State Med Soc. 1998;150(4):138–41.
10. Foltran F, Ballali S, Passali FM, Kern E, Morra B, Passali GC, et al. Foreign bodies in the airways: a meta-analysis of published papers. Int J Pediatr Otorhinolaryngol. 2012;76(Suppl 1):S12–9.
11. Korraa E, Madkour A, Wagieh K, Nafae A. Bronchoscopic foreign body extraction in a pulmonary medicine department: a retrospective review of egyptian experience. J Bronchol Interv Pulmonol. 2010;17(1):39–44.
12. Committee on Injury V, Poison P. Prevention of choking among children. Pediatrics. 2010;125(3):601–7.
13. Centers for Disease C, Prevention. Toy-related injuries among children and teenagers–United States, 1996. MMWR Morb Mortal Wkly Rep. 1997;46(50):1185–9.
14. Abdel-Rahman HA. Fatal suffocation by rubber balloons in children: mechanism and prevention. Forensic Sci Int. 2000;108(2):97–105.
15. Bolton SM, Saker M, Bass LM. Button battery and magnet ingestions in the pediatric patient. Curr Opin Pediatr. 2018;30(5):653–9.
16. Yang W, Jones M, Mallick S. Tracheo-oesophageal fistula: a delayed complication of missed inhaled magnetic toys. J Surg Case Rep. 2018;2018(2):rjy022.
17. McLarty JD, Krishnan M, Rowe MR. Disk battery aspiration in a young child: a scarcely reported phenomenon. Arch Otolaryngol Head Neck Surg. 2012;138(7):680–2.
18. Johnson K, Linnaus M, Notrica D. Airway foreign bodies in pediatric patients: anatomic location of foreign body affects complications and outcomes. Pediatr Surg Int. 2017;33(1):59–64.
19. Baharloo F, Veyckemans F, Francis C, Biettlot MP, Rodenstein DO. Tracheobronchial foreign bodies: presentation and management in children and adults. Chest. 1999;115(5):1357–62.
20. Black RE, Johnson DG, Matlak ME. Bronchoscopic removal of aspirated foreign bodies in children. J Pediatr Surg. 1994;29(5):682–4.
21. Eren S, Balci AE, Dikici B, Doblan M, Eren MN. Foreign body aspiration in children: experience of 1160 cases. Ann Trop Paediatr. 2003;23(1):31–7.
22. Lima JA. Laryngeal foreign bodies in children: a persistent, life-threatening problem. Laryngoscope. 1989;99(4):415–20.
23. Esclamado RM, Richardson MA. Laryngotracheal foreign bodies in children. A comparison with bronchial foreign bodies. Am J Dis Child. 1987;141(3):259–62.
24. Sink JR, Kitsko DJ, Georg MW, Winger DG, Simons JP. Predictors of foreign body aspiration in children. Otolaryngol Head Neck Surg. 2016;155(3):501–7.
25. Wiseman NE. The diagnosis of foreign body aspiration in childhood. J Pediatr Surg. 1984;19(5):531–5.
26. Even L, Heno N, Talmon Y, Samet E, Zonis Z, Kugelman A. Diagnostic evaluation of foreign body aspiration in children: a prospective study. J Pediatr Surg. 2005;40(7):1122–7.
27. Mu L, He P, Sun D. The causes and complications of late diagnosis of foreign body aspiration in children. Report of 210 cases. Arch Otolaryngol Head Neck Surg. 1991;117(8):876–9.
28. Saquib Mallick M, Rauf Khan A, Al-Bassam A. Late presentation of tracheobronchial foreign body aspiration in children. J Trop Pediatr. 2005;51(3):145–8.
29. Hitter A, Hullo E, Durand C, Righini CA. Diagnostic value of various investigations in children with suspected foreign body aspiration: review. Eur Ann Otorhinolaryngol Head Neck Dis. 2011;128(5):248–52.
30. DeBoer EM, Prager JD, Kerby GS, Stillwell PC. Measuring pediatric bronchoscopy outcomes using an electronic medical record. Ann Am Thorac Soc. 2016;13(5):678–83.
31. Giddings CE, Rimmer J, Weir N. Chevalier Jackson: pioneer and protector of children. J Laryngol Otol. 2013;127(7):638–42.
32. Panchabhai TS, Mehta AC. Historical perspectives of bronchoscopy. Connecting the dots. Ann Am Thorac Soc. 2015;12(5):631–41.
33. Wood RE. The emerging role of flexible bronchoscopy in pediatrics. Clin Chest Med. 2001;22(2):311–7. viii
34. Wood RE, Gauderer MW. Flexible fiberoptic bronchoscopy in the management of tracheobronchial foreign bodies in children: the value of a combined approach with open tube bronchoscopy. J Pediatr Surg. 1984;19(6):693–8.
35. Wood RE, Sherman JM. Pediatric flexible bronchoscopy. Ann Otol Rhinol Laryngol. 1980;89(5):414–6.
36. Tenenbaum T, Kahler G, Janke C, Schroten H, Demirakca S. Management of foreign body removal in children by flexible bronchoscopy. J Bronchol Interv Pulmonol. 2017;24(1):21–8.
37. Fidkowski CW, Zheng H, Firth PG. The anesthetic considerations of tracheobronchial foreign bodies in children: a literature review of 12,979 cases. Anesth Analg. 2010;111(4):1016–25.
38. Tang LF, Xu YC, Wang YS, Wang CF, Zhu GH, Bao XE, et al. Airway foreign body removal by flexible bronchoscopy: experience with 1027 children during 2000–2008. World J Pediatr. 2009;5(3):191–5.
39. Ramirez-Figueroa JL, Gochicoa-Rangel LG, Ramirez-San Juan DH, Vargas MH. Foreign body removal by flexible fiberoptic bronchoscopy in infants and children. Pediatr Pulmonol. 2005;40(5):392–7.
40. Limper AH, Prakash UB. Tracheobronchial foreign bodies in adults. Ann Intern Med. 1990;112(8):604–9.
41. Lan RS, Lee CH, Chiang YC, Wang WJ. Use of fiberoptic bronchoscopy to retrieve bronchial foreign bodies in adults. Am Rev Respir Dis. 1989;140(6):1734–7.
42. Swanson KL, Prakash UB, Midthun DE, Edell ES, Utz JP, McDougall JC, et al. Flexible bronchoscopic management of airway foreign bodies in children. Chest. 2002;121(5):1695–700.
43. Leonard J, Jankowska A, Baik M, Kazachkov M. Anesthetic management of an extremely premature, extremely low-birth-weight infant undergoing

bronchoscopy for removal of an aspirated foreign body. A A Case Rep. 2015;5(10):185–7.
44. Nandalike K, Kessel A, Tripathi S, Sweberg T, Vicencio AG. Foreign body aspiration in a child with unilateral lung aplasia. Pediatr Crit Care Med. 2011;12(5):e216–8.
45. Singh JK, Vasudevan V, Bharadwaj N, Narasimhan KL. Role of tracheostomy in the management of foreign body airway obstruction in children. Singap Med J. 2009;50(9):871–4.
46. Tamiru T, Gray PE, Pollock JD. An alternative method of management of pediatric airway foreign bodies in the absence of rigid bronchoscopy. Int J Pediatr Otorhinolaryngol. 2013;77(4):480–2.
47. Soodan A, Pawar D, Subramanium R. Anesthesia for removal of inhaled foreign bodies in children. Paediatr Anaesth. 2004;14(11):947–52.
48. Berg MD, Schexnayder SM, Chameides L, Terry M, Donoghue A, Hickey RW, Berg RA, Sutton RM, Hazinski MF; American Heart Association. Pediatric basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics. 2010;126(5):e1345–60.
49. Mani N, Soma M, Massey S, Albert D, Bailey CM. Removal of inhaled foreign bodies--middle of the night or the next morning? Int J Pediatr Otorhinolaryngol. 2009;73(8):1085–9.
50. She YJ, Tan YH, Zhang YF. Two different anesthesia and ventilation for removal of airway foreign bodies in 240 children. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2010;45(7):599–601.
51. Kazachkov M, Vicencio A. Foreign body removal is getting "cooler". Pediatr Pulmonol. 2016;51(9):886–8.
52. Wang L, Zhang L, Li D, Li C, Wang Y, Gao M, et al. Successful retrieval of a plastic bead from the airway of a child by flexible bronchoscopy and a balloon-tipped catheter: a case report and literature review. Medicine (Baltimore). 2018;97(37):e12147.
53. McAfee SJ, Vashisht R. Removal of an impacted distal airway foreign body using a guidewire and a balloon angioplasty catheter. Anaesth Intensive Care. 2011;39(2):303–4.
54. Wong KS, Lai SH, Lien R, Hsia SH. Retrieval of bronchial foreign body with central lumen using a flexible bronchoscope. Int J Pediatr Otorhinolaryngol. 2002;62(3):253–6.
55. Elsharkawy H, Abd-Elsayed AA, Karroum R. Management challenges in the passing-through technique using a fogarty catheter to remove an endobronchial foreign body from an infant. Ochsner J. 2015;15(1):110–3.
56. Soong WJ, Tsao PC, Lee YS, Yang CF, Liao J, Jeng MJ. Retrieving difficult aspirated pen caps by balloon catheter with short working-length flexible endoscopy and noninvasive ventilation support in intensive care unit. Int J Pediatr Otorhinolaryngol. 2015;79(9):1484–9.
57. Hockstein NG, Jacobs IN. Flexible bronchoscopic removal of a distal bronchial foreign body with cinefluoroscopic guidance. Ann Otol Rhinol Laryngol. 2004;113(11):863–5.
58. Aggarwal SK, Sinha SK, Ratan SK, Dhua A, Sethi GR. Complications of long-standing foreign body in the airway and their outcomes after endoscopic management: an experience of 20 cases. J Laparoendosc Adv Surg Tech A. 2015;25(1):81–7.
59. Tan GX, Boss EF, Rhee DS. Bronchoscopy for pediatric airway foreign body: thirty-day adverse outcomes in the ACS NSQIP-P. Otolaryngol Head Neck Surg. 2019;160(2):326–31.
60. Zhang L, Yin Y, Zhang J, Zhang H. Removal of foreign bodies in children's airways using flexible bronchoscopic CO2 cryotherapy. Pediatr Pulmonol. 2016;51(9):943–9.
61. Tomaske M, Gerber AC, Weiss M. Anesthesia and periinterventional morbidity of rigid bronchoscopy for tracheobronchial foreign body diagnosis and removal. Paediatr Anaesth. 2006;16(2):123–9.

Laryngotracheal Stenosis

26

Aileen Wertz, Steven Sobol, and Luv Javia

Anatomic Review

The larynx is divided into the supraglottis, glottis, and subglottis. The supraglottis includes the epiglottis, arytenoid towers, aryepiglottic folds, and false vocal folds. The glottis begins at the superior surface of the vocal folds and ends 1 cm below the superior surface of the vocal folds. The subglottis begins at the inferior extent of the glottis and ends at the inferior extent of the cricoid cartilage. The trachea begins where the subglottis ends. The hyoid bone and thyroid and cricoid cartilages provide external support to the larynx and subglottis while the tracheal rings perform this task for the trachea. The epiglottis and arytenoid towers contain cartilaginous support. The corniculate and cuneiform cartilages sit above the arytenoid cartilages and provide additional rigidity to the aryepiglottic folds [1]. See Fig. 26.1 for an example of a normal larynx on endoscopic examination. See Fig. 26.2 for a review of normal laryngeal framework anatomy.

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Branches of the vagus nerve, cranial nerve X, provide sensory and motor innervation to the larynx and trachea. The superior laryngeal nerve has internal and external branches. The internal branch provides sensory innervation to the larynx and pierces the lateral thyrohyoid membrane to exit the larynx. The external component provides motor innervation to the cricothyroid muscles and inferior esophageal constrictor. The cricothyroid muscles change voice pitch by shortening and lengthening the vocal cords [1].

The recurrent laryngeal nerve provides motor input to the remainder of the intrinsic laryngeal muscles, which are thyroarytenoid, posterior cricoarytenoid, lateral cricoarytenoid, and interarytenoid. The interarytenoid is the only muscle that is not paired. The medial aspect of the thyroarytenoid muscle is also called the vocalis muscle. The recurrent laryngeal nerve branches off the vagus nerve in the chest and travels around the subclavian artery on the right and the ligamentum arteriosum on the left. The recurrent laryngeal nerves then travel within the tracheoesophageal grooves in the neck and enter the larynx at the cricothyroid joint [1].

Embryology and Histology

The embryology and histology of the larynx and trachea are important because pediatric pathology is often caused by errors in embryologic develop-

S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_26

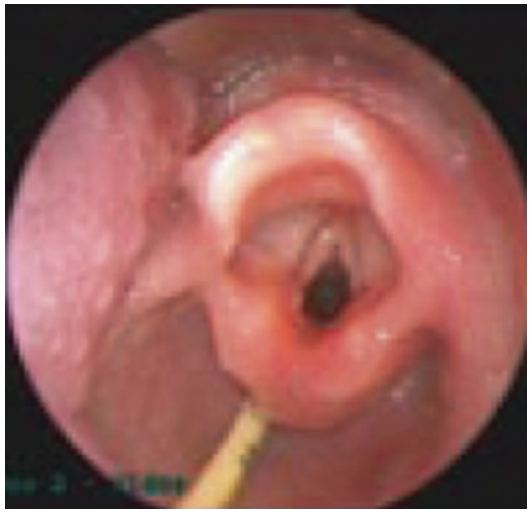

Fig. 26.1 Ariel view of larynx from pharynx showing normal supraglottic, glottic, and subglottic anatomy

ment, or post-utero aberration of normal histology. The laryngeal cartilages, musculature, and superior and recurrent laryngeal nerves are formed from branchial arches IV and VI. At the fourth week of development, the foregut (primitive pharynx) begins to develop ventral and dorsal outgrowths separated by the tracheoesophageal septum. The ventral portion (respiratory primordium) develops into the larynx, trachea, and lungs. The dorsal portion develops into the esophagus. Normally, the respiratory primordium lumen is obliterated by epithelial proliferation then recanalizes by the tenth week of development [1].

The larynx and trachea are lined by respiratory epithelium, which is pseudostratified ciliated columnar, except at the level of the vocal cords where the epithelial lining is stratified squamous cells. Minor salivary glands and mesenchymal structures, such as the synovial cricoarytenoid joint, are rare, but possible, sources of pathology as well.

Etiologies of Stenosis

While some causes of stenosis can occur at multiple levels within the airway, specific pathologies are often associated with a specific portion of the larynx or trachea.

A. *Supraglottic Stenosis*

(i) *Laryngeal Atresia*

This is caused by a failure of the larynx to recanalize in utero. It presents as CHAOS (Congenital High Airway Obstruction Syndrome) characterized by enlarged lungs, inverted diaphragms, polyhydramnios, and ascites. It can be diagnosed by fetal MRI. It requires tracheostomy prior to separation from maternal circulation, known as an EXIT procedure (EX-utero Intrapartum Treatment) [2].

(ii) *Caustic Ingestion*

Ingestion of alkali or acid chemicals as well as inhalation burns can all cause laryngeal stenosis due to scarring. These are rare events, but late stenosis due to laryngeal mucosal injury must be kept in mind when laryngeal injury due to caustic materials is diagnosed at the time of initial exposure. Caustic ingestion can also cause tracheal injury in concert with laryngeal injury, or isolated to the trachea if by adjacent extension of esophageal injury.

(iii) *Venolymphatic Malformations*

Internal masses of the airway narrow it as do external masses via compression of the airway. Such masses can occur anywhere along the airway but are mentioned here as venolymphatic malformations most often affect the supraglottic structures. When large, they may be diagnosed in utero and present with respiratory distress at birth. If the mass is smaller, it may not present until it enlarges due to infection. Children may also present with sporadic or positional symptoms. For example, a venous malformation may expand with crying causing symptoms only with crying and may not even be visible at other times [3].

There are many other masses that can narrow the larynx and trachea. It is beyond the scope of this chapter to discuss each one. Other congenital masses to consider are teratoma, hamartoma, and

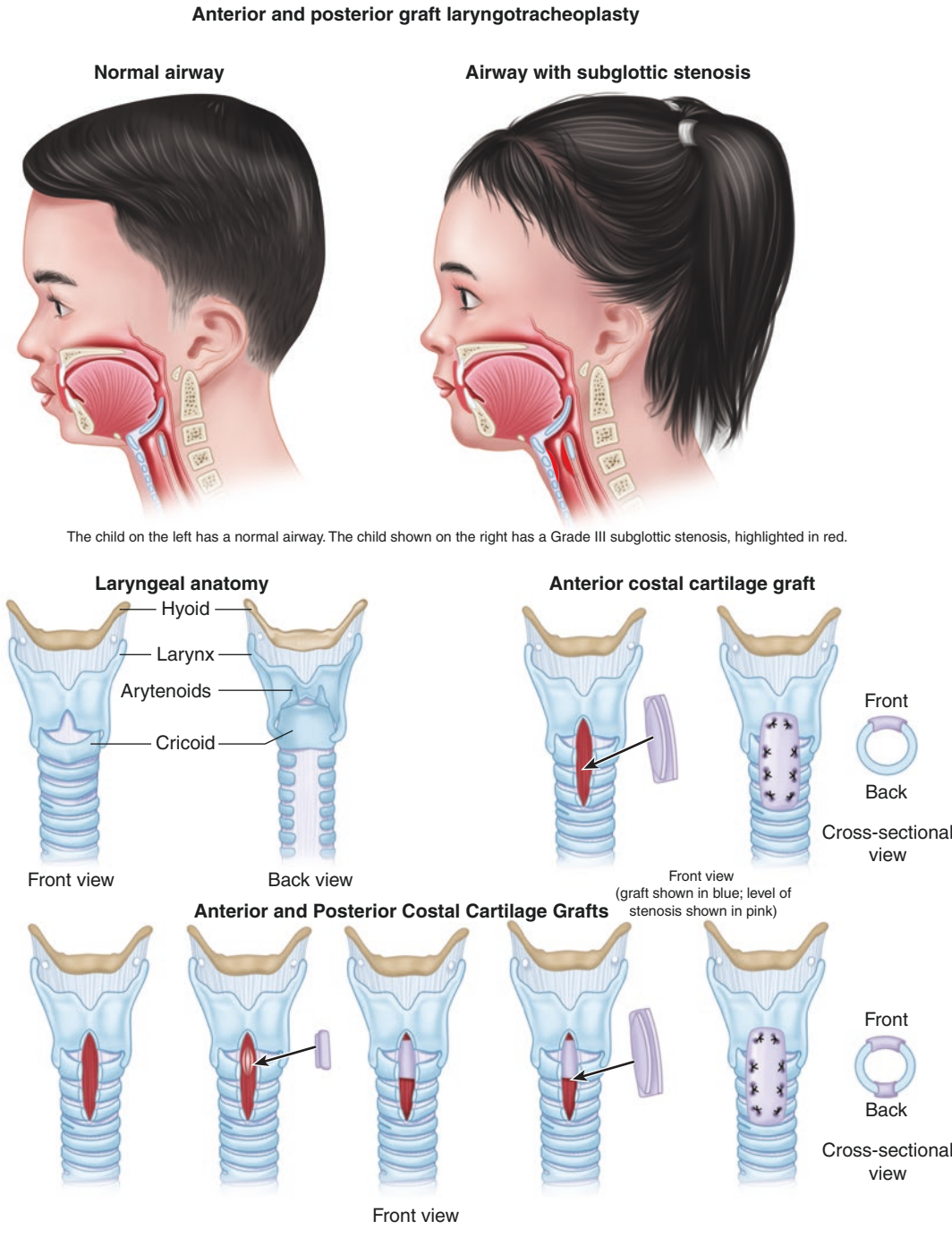

Fig. 26.2 Artist's rendering of normal laryngeal anatomy and the steps of laryngotracheal reconstruction

foregut duplication cyst. Acquired masses can arise from any tissue within or adjacent to the airway and can be infectious, inflammatory, or neoplastic and include granulomatous disease, lymphoma, sarcoma, minor salivary tumors, thyroid tumors, and fungal infections, among others. If a patient's presentation

or airway examination appear atypical, it is important to consider less common pathology and have a low threshold for multidisciplinary workup of the pathology.

B. *Glottic Stenosis*

(i) *Bilateral Vocal Fold Motion Impairment*

When both vocal folds are immobile, the glottic aperture is often narrowed such that stridor and increased work of breathing are present. While glottic narrowing is possible with a unilateral vocal fold immobility, it is much less likely. Etiology of vocal fold immobility can be neurologic (causing paresis or paralysis) or structural. Paresis indicates reduction in motion with some motion still present while paralysis indicates complete immobility. Nerve injury can occur anywhere along the vagus nerve's path from brain stem to recurrent laryngeal branching points and along the recurrent laryngeal nerves. Because of this, imaging from the brainstem through the upper chest is required for idiopathic focal fold immobility. Bilateral, neurologic vocal fold immobility is most often due to brainstem compression such as a Chiari malformation. Common structural etiologies involve scarring of the cricoarytenoid joints and congenital webs.

(ii) *Laryngeal Web*

This a membranous connection, classically between the anterior portions of the focal folds resulting in a narrowed glottic aperture of varying severity. They can be congenital due to incomplete recanalization of the larynx during development, or they can be iatrogenic due to intubation or surgical trauma. Congenital webs are associated with 22q11 genetic mutations. See Fig. 26.3 for an endoscopic appearance of a congenital anterior web.

(iii) *Posterior Glottic Stenosis*

While this can also be caused by incomplete recanalization in utero like the more classic anterior laryngeal web, it is quite rare. Congenital cricoid cartilage abnormalities can affect the posterior glottic aperture as well, but subglottic narrowing would also be expected. Most commonly, posterior glottic stenosis is due to scar formed in response to trauma associated with intubation, surgical, or accidental trauma [1]. See Fig. 26.4 for an example of posterior glottic stenosis due to trauma to the area.

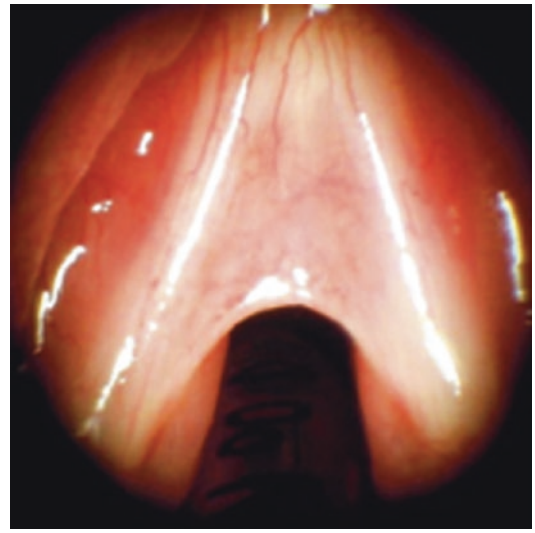

Fig. 26.3 Anterior glottic web, congenital

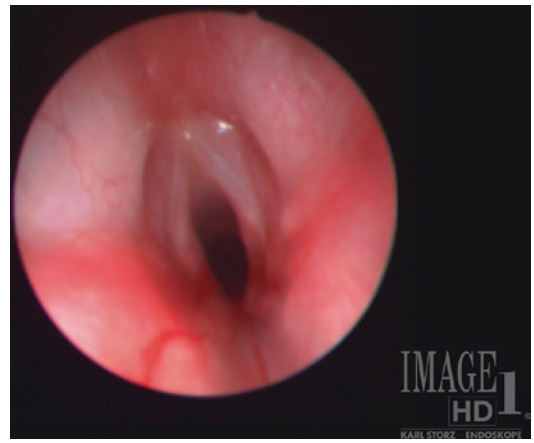

Fig. 26.4 Posterior glottic stenosis, acquired

C. *Subglottic Stenosis*

(i) *Congenital*

Congenital stenosis is due to malformation of the cricoid cartilage causing it to be elliptical rather than ring-shaped. The cricoid cartilage is often found to be fused with the first tracheal ring during surgery as part of the malformation of the cricoid cartilage. The endoscopic appearance of the stenosis tends to be more elliptical, in keeping with the cartilaginous configuration, rather than the circumferential appearance of acquired subglottic stenosis (Fig. 26.5a).

Congenital subglottic stenosis tends to be less severe than acquired stenosis. It can present as recurrent croup with stridor in a young child or exercise intolerance in an older child [1]. Croup in a child under 6 months or recurrent croup in a child 1–2 years old should raise suspicion for subglottic stenosis, or other airway pathology. Subglottic stenosis can also present as an inability to intubate a patient with an age-appropriate endotracheal tube.

(ii) *Acquired*

Acquired stenosis can be due to any iatrogenic cause of subglottic trauma but is classically due to prolonged intubation in the neonatal period. The hypothesized pathogenesis is that the endotracheal tube causes pressure necrosis of the mucosa of the subglottis, especially posteriorly, which then results in an inflammatory response leading to chondritis with subsequent cartilage remodeling and mucosal scar at the interarytenoid, glottic, and subglottic levels [4, 5]. Figure 26.5b shows a mature, acquired subglottic stenosis. It is described as mature because the scar appears indolent without acute edema or inflammation, which is associated with immature, or still evolving, subglottic stenosis.

It can present in the same ways as congenital stenosis, or as an inability to extubate or wean from positive pressure ventilatory support despite resolving primary pulmonary pathology that necessitated intubation originally.

A 2001 review found 2% of babies admitted to the NICU develop subglottic stenosis and over half of those that develop it were very low birth weight infants [6]. Other factors thought to explain why some neonates develop subglottic stenosis while others do not despite similar lengths of intubation include laryngopharyngeal reflux, multiple intu-

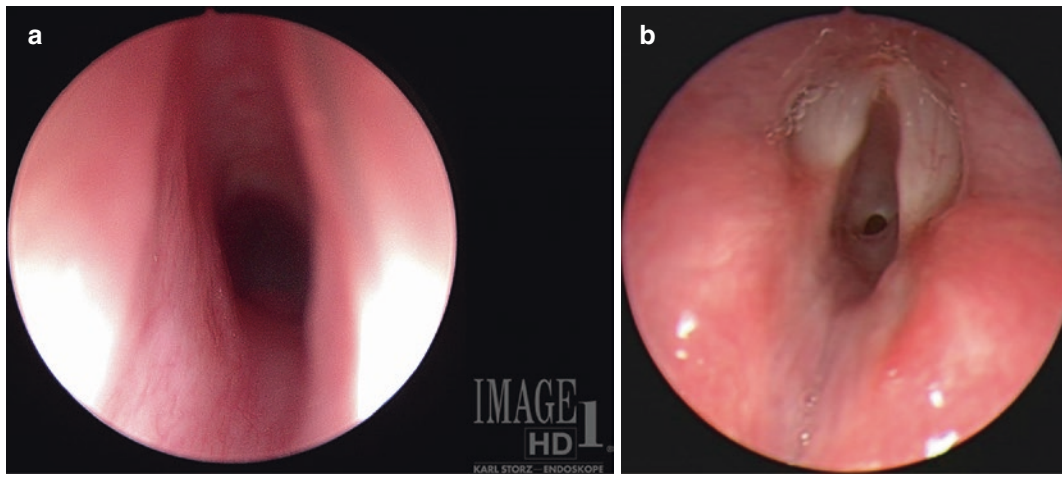

Fig. 26.5 Subglottic stenosis. (**a**) Congenital. Elliptical with lateral shelves. (**b**) Acquired. Circumferential within more circular airway

bations, traumatic intubations, and mobility of the endotracheal tube throughout intubation [7, 8].

(iii) *Hemangioma*

Hemangiomas are not vascular malformations, but rather benign vascular tumors characterized by disordered angiogenesis. They are absent at birth, then proliferate for 6–9 months. This is followed by involution to a varying degree over the next couple of years. Hemangiomas can be present anywhere on the body and are most commonly cutaneous. While subglottic hemangiomas are rare, it is very important to delineate them from other causes of subglottic narrowing as hemangiomas are usually cured with propranolol with or without steroids. In contrast to other causes of subglottic stenosis, hemangiomas are quite compressible and have a submucosal, vascular appearance. They are often posteriorly based, eccentric to the right [1] (Fig. 26.6).

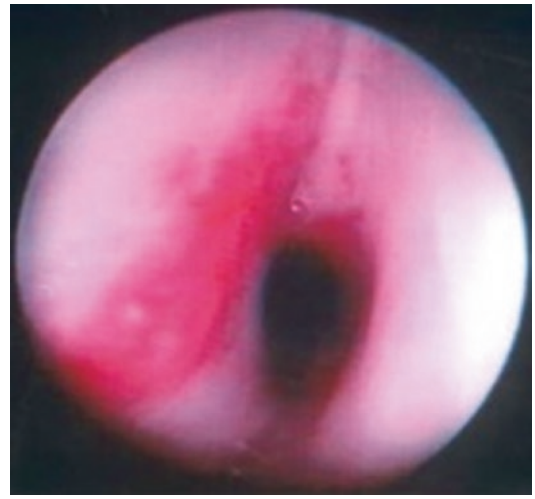

Fig. 26.6 Subglottic hemangioma. Note the vascular staining. These are soft and compressible when instrumented allowing for safe intubation by a trained physician without bleeding, if intubation required

D. *Tracheal Stenosis*

Tracheal stenosis is very rare with an incidence of 1 in 64,500 births. It represents only 0.3–1% of all laryngotracheal stenoses [9]. Similar to stenosis of the larynx, it can be broken down into general categories of external compression, cartilaginous framework abnormalities with and without mucosal scar, and isolated mucosal scar.

(i) *Complete Rings*

This term indicates the cartilaginous ring of the trachea is present for the entire circumference of the trachea at that level as compared to the normal cartilaginous tracheal ring, which is only present along the anterior 2/3 of the trachea with the trachealis muscle comprising the posterior component of the trachea (see Fig. 26.7). It is the most common cause of tracheal stenosis [9]. Patients with Trisomy 21 are at increased risk of this developmental anomaly. Complete rings can occur in isolation, but more commonly, about 60% of the time, occur in association with cardiovascular and other airway anomalies.

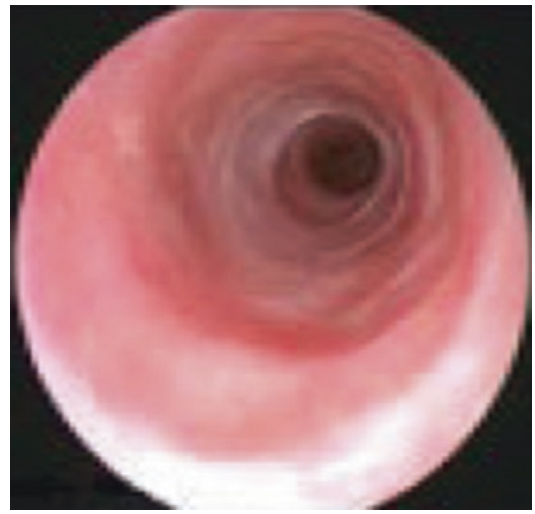

Fig. 26.7 Complete tracheal rings

Pulmonary artery sling, described below, is the most commonly associated abnormality; 20% of the time patients with complete tracheal rings also have subglottic stenosis [10]. It is essential to assess for the presence of bronchomalacia or bronchial stenosis as both are also seen in association with tracheal stenosis and impact postoperative outcomes [11].

While the presentation of tracheal stenosis overlaps with that of subglottic stenosis, tracheal stenosis is more likely to present with biphasic stridor with a prominent expiratory component and a wet sound described as "washing machine breathing" due to inability to clear secretions from the narrowed trachea.

Speggiorin et al. developed a classification system that is helpful in describing the stenosis, which in turn assists in treatment planning. The most common patterns described by their group include progressive narrowing of the stenosis more distal in the trachea with the majority of the trachea involved, short segment stenosis in the mid-trachea, and tracheal stenosis of the tracheal segment between a pseudo-carina (pig bronchus or bronchus suis) and the true carina [12].

(ii) *Tracheal Cartilaginous Sling*

Tracheal sling is a rare congenital abnormality in which the cartilaginous tracheal rings are fused together forming a sheet of cartilage instead of discrete rings. This causes luminal narrowing of varying severity depending on whether the fused rings are C- or O-shaped and the length of segment is affected. It is seen in patients with craniosynostosis syndromes and has a historically poor prognosis with 90% mortality rate by 2 years of age. The poor prognosis is attributed to multilevel airway obstruction in these patients and the inherent challenges in improving this type of airway stenosis, as both tracheostomy and slide tracheoplasty are technically challenging [13–15].

(iii) *Absent Tracheal Rings*

This is a rare entity within the already rare entity of tracheal stenosis. It is not associated with other abnormalities. Its presentation and management are similar to complete tracheal rings except that on bronchoscopy there is a complete lack of cartilage at the site of abnormality [16].

(iv) *Vascular Rings and Slings*

These abnormalities externally compress the airway resulting in malacia and narrowing of the airway at the site of compression. Presentation often includes need for positive pressure ventilation without primary lung pathology and biphasic stridor and increased work of breathing similar to that seen with complete rings. On bronchoscopy, it is important to look for pulsatility and any eccentric narrowing of the trachea. An abnormal innominate artery that branches more distal than usual is the most common vascular cause of tracheal compression.

Vascular rings are caused by aberrant aortic arch anatomy, such as a double aortic arch. The most common vascular sling is caused by aberrant pulmonary artery anatomy such that the left pulmonary artery originates from the right pulmonary artery, passing between the trachea and esophagus, resulting in compression [1].

(v) *Acquired*

Acquired tracheal stenosis can occur by the same mechanisms as subglottic stenosis described above. It can also occur after tracheostomy at, or just above, the tracheostomy site. This is called an "A-frame deformity" due to the classic appearance of the tracheal lumen on bronchoscopy. It is due to breakdown of the cartilaginous ring framework at the site of the tracheostomy (Fig. 26.8).

Diagnosing Stenosis

Suspicion for laryngotracheal stenosis should be maintained at a high level because of the variability in symptom and sign severity. In addition, the risks of clinical workup for stenosis are small in comparison to the risks of missed stenosis with subsequent complications. As with all clinical assessments, a detailed history and physical

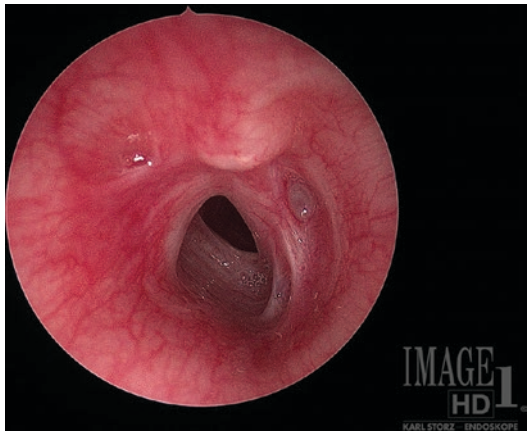

Fig. 26.8 A-frame deformity of the trachea. In addition to classic A-framing of the airway, there is an anterior scar proximally and a posterior scar more distally

examination is the first step. Looking at and listening to the patient's respiratory pattern can provide a great deal of information regarding the severity and location of turbulent flow due to airway narrowing. Classically, supraglottic and glottic stenosis cause inspiratory stridor, subglottic and tracheal stenosis causes biphasic stridor, while bronchial and primary pulmonary pathology causes expiratory turbulence. While the use of accessory muscles for respiration, commonly referred to as "retractions," can be seen with all causes of airway narrowing, the level of greatest accessory muscle use may indicate the area of greatest narrowing.

Plain film imaging of the neck in lateral and anterior–posterior orientations can identify narrowing of the airway and is used regularly to look for acute subglottic narrowing in children suspected to have croup. The gold standard for diagnosis of laryngotracheal stenosis is laryngoscopy and bronchoscopy.

Once it has been determined that airway stenosis is present, it is important to characterize and understand the stenosis as thoroughly as possible. Important details to identify and describe include specific anatomic level of stenosis, total length of stenosis, severity, or grade of stenosis, shape of stenosis, working hypothesis of etiology, and character of stenosis.

Level can be described using the anatomic terminology reviewed above and should be as specific as possible. Both length and grade of stenosis can be measured during bronchoscopy, using bronchoscope or rigid telescope and a ruler. Grade of subglottic stenosis should be described using the Cotton-Myer scale where grade I is a stenosis up to 50%, grade II is 51–70%, grade III is 71–99%, and grade IV is no detectable lumen [17]. For other airway levels, the percent stenosis can be approximated. The character of the stenosis, soft or firm, thin or thick, is important to note, as it indicates whether the stenosis is mature or evolving and what treatment modalities may be effective.

When diagnosing and assessing stenosis, it is important to keep instrumentation and trauma to a minimum. Very little force can cause trauma to the stenosis and very little edema can result in critical airway obstruction. It is always preferred to incompletely assess a stenosis rather than traumatize the area. It is important to consider how distal the stenosis extends and how severe it is when considering intubation and tracheostomy during the acute presentation. Neither intervention is likely to be efficacious if the stenosis involves the intrathoracic trachea, which is the case for 90% of tracheal stenoses [10]. In such cases, balloon dilation may temporize respiratory distress and ECMO may need to be considered and mobilized. Shallow intubation with the endotracheal tube sitting above the stenosis may temporize an emergent situation. Patients intubated this way will require longer inspiratory and expiratory times and increased peak pressures to adequately ventilate past the stenosis.

Managing Stenosis

Multidisciplinary team approach to care of patients with laryngotracheal stenosis results in improved clinician understanding of the interconnectedness of aerodigestive pathologies while providing the highest quality, comprehensive care. Additionally, cost savings and reduced inpatient stays have been found to be associated with a multidisciplinary care team approach [18, 19].

A. *Multidisciplinary Team Components*

Healthcare personnel included in multidisciplinary aerodigestive teams include otolaryngologists, gastroenterologists, pulmonologists, speech language pathologists, care coordinators, respiratory therapists, social workers, occupational therapists, and sleep medicine physicians.

Events performed in a multidisciplinary manor include case conference where patients are discussed before and/or after they have been assessed by each team member. This often occurs at the beginning and/or end of a multidisciplinary clinic day where all, or most, providers listed above see the patient in sequence or together depending on what works best. Operative procedures are also grouped into one visit and anesthetic and most often include flexible bronchoscopy, rigid laryngoscopy and bronchoscopy, and esophagogastroduodenoscopy.

Some benefits of 1 operative event that includes all required specialist workups include reduced anesthesia and operating room costs, improved family experience due to receiving the assessment and plan of all teams at the same time in a coordinated manner, and improved team member understanding of the patient's global clinical picture [20, 21].

B. *Immediate Stenosis Management*

When a patient first presents with laryngotracheal stenosis, the initial assessment and plan are informed by the patient's overall stability and clinical picture. It is important to consider if the airway stenosis is evolving or may evolve and the risks and benefits of delaying intervention. If the stenosis is thought to be evolving, it is important to consider if it may narrow further and what intervention may be needed prior to further narrowing.

Broadly speaking, it needs to be decided if the stenosis requires intervention or not. If intervention is required, then is medical management adequate or is surgical intervention needed. Further, is emergent or scheduled surgical intervention indicated. These clinical decisions along with the nature and etiology of the stenosis inform the initial management, which can range from active surveillance to emergent tracheostomy or balloon dilation. A general rule is that grade I stenosis and some grade II stenosis (stenosis obstructing <70% of the airway) may be managed conservatively if symptoms and comorbid conditions allow while stenosis obstructing 70% or more of the airway will require surgical intervention.

Medical management of an evolving, immature, or inflamed stenosis often includes intravenous steroids, humidified air with or without positive pressure, anti-reflux therapy, racemic epinephrine breathing treatments, and a mixture of helium and oxygen, called heliox. Heliox increases laminar flow, decreasing work of breathing from proximal airway obstruction.

Evidence supporting the treatment of gastro- and extra-esophageal reflux comes primarily from animal and adult studies of subglottic stenosis, as the data regarding reflux treatment in pediatric laryngotracheal stenosis are limited. One animal study found reflux contents to cause scarring of a previously injured subglottis [22]. Gastroesophageal reflux treatment has also been shown to improve response to balloon dilation in adults with idiopathic subglottic stenosis [23].

Gastroesophageal reflux is thought to affect both acquired stenosis and postoperative healing via extra-esophageal reflux of gastric and/or duodenal contents onto the larynx, called laryngopharyngeal reflux. While many studies have been published regarding laryngopharyngeal reflux in adults, the impact of gastroesophageal reflux management on laryngotracheal reconstruction (LTR) success rates remains controversial. Given the significant morbidity associated with LTR failure, however, most aerodigestive surgeons advocate for the use of acid suppression during the perioperative period.

C. *Long-Term Stenosis Management*

(a) *Preoperative*

If a patient requires surgical intervention to correct their laryngotracheal stenosis, it is important to ensure they are optimized prior to scheduling reconstruc-

tive airway surgery. The primary areas in need of preoperative optimization include lung function, pulmonary clearance, airway inflammation, aspiration, and laryngopharyngeal reflux.

Flexible bronchoscopy with bronchoalveolar lavage is vital to assessing the airway's readiness for reconstruction and what can be done to optimize the patient. During flexible bronchoscopy, assessment for an "active larynx" is performed. Signs of an active larynx include nodularity, lymphoid hyperplasia, and edema. An active larynx indicates laryngopharyngeal reflux and/or chronic bronchitis are present and should be treated prior to reconstructive surgery.

Flexible bronchoscopy is also excellent for assessing if there are other sites of obstruction in addition to the laryngotracheal stenosis that may require attention, such as pharyngeal collapse or airway malacia. Secondary obstructions may be dynamic or fixed. Flexible bronchoscopy with minimal anesthesia via dexmedetomidine, spontaneous ventilation, and little-to-no ventilatory assistance is best suited to identify dynamic collapse [24].

It is best if bronchoalveolar lavage occurs prior to otolaryngologic and gastroenterology procedures to avoid specimen contamination; however, if intubation is required for lavage then rigid bronchoscopy should occur first as an endotracheal tube will alter the appearance of the airway, especially at a site of stenosis. Timing of airway reconstruction, need for preoperative antibiotics, and change in reflux management are each informed by flexible bronchoscopy with bronchoalveolar lavage findings [25].

(b) *Postoperative*

Pulmonary expertise and flexible bronchoscopy are important after airway reconstructive surgery as well. In the immediate postoperative period, pulmonary expertise in managing mucous clearance and comorbid lung disease is necessary given the increased secretions and decreased pulmonary clearance associated with surgery. In addition, many patients have comorbid chronic lung disease or reactive airway disease. Long-term, pulmonary assessments are key in determining when a patient is ready for tracheostomy decannulation if a staged procedure was performed.

D. *Surgical Airway Reconstruction*

There are many techniques described to treat laryngotracheal stenosis of various etiologies and characteristics. Here, a brief description of the most common surgical procedures is provided focusing on practical anatomic changes and management options for each.

(a) *Endoscopic Balloon Dilation*

The frequency with which balloon dilation is utilized varies by center. It is thought to be most useful in soft, evolving stenosis and grade I–II stenosis. It is often performed with adjuvant treatment, such as steroid or mitomycin application, or with additional tissue removal with powered microdebriders, knifes, and laser ablation, each of which can also be used alone.

The data regarding success of these endoscopic approaches are heterogeneous and difficult to synthesize given the patient population is heterogeneous and relatively small, and that the there are many permutations of endoscopic treatment. A recent systematic review included 22 studies and found the success rate ranged from 50 to 100% for balloon dilation with and without adjuvant endoscopic therapy [26]. A meta-analysis that only included 7 studies found a success rate of 65%, but average follow-up was only 4.6 months [27]. Success was defined as decannulation and no need for open reconstruction in both studies.

(b) *Cricoid Split*

This procedure can be performed endoscopically or open through a midline ante-

rior neck incision. It involves cutting the mucosa and cricoid cartilage. Both anterior and posterior cuts can be made or just one or the other. Patients are often intubated with a slightly larger endotracheal tube for 3–14 days after the procedure to allow healing of the cricoid cartilage with a wider circumference. This technique has been shown to adequately treat congenital bilateral vocal cord immobility, avoiding the need for tracheostomy in appropriately selected patients [28].

(c) *Laryngotracheal Reconstruction (LTR)*

LTR is the most common open airway reconstruction. It treats subglottic stenosis primarily but can also improve glottic stenosis and high tracheal stenosis. Traditionally, it requires a midline neck incision with exposure of the laryngeal framework; however, endoscopic approaches to posterior cricoid graft placement are also performed. The cricoid cartilage is always opened, or split, with the inclusion of tracheal and thyroid cartilage incisions determined by the level and length of the stenosis. After incisions are made to open the stenotic portion of the airway, grafts are placed to further open the airway.

LTRs are delineated as single versus double stage. Single stage indicates no tracheostomy tube is present at the end of the LTR. Double stage indicates a tracheostomy is left in place distal to the stenosis in anticipation of decannulation once the LTR site has healed 1 month or longer after the LTR. Additionally, it is delineated where grafts were placed with the options being anteriorly, posteriorly, or both anterior and posterior. Anterior and posterior indicate where within the cricoid cartilage the grafts were placed. See Fig. 26.2 for an illustration of anterior and posterior graft placement.

Grafts are carved from cartilage, most commonly harvested from a rib, but thyroid alar cartilage can also be used when a relatively small volume of cartilage is needed. Thyroid alar grafts are classically used in infants undergoing LTR; however, it is a good match for reconstruction whenever it can provide a graft large enough to stent open the airway. Auricular cartilage can also be used in rare instances where a small and relatively thin graft is adequate.

LTR can be performed on very young infants, similar to cricoid split alone, and can avoid tracheostomy in appropriately selected infants [29]. Cardiopulmonary and neurologic comorbid conditions are important to consider when making this determination, as successful cases of LTR in young infants usually do not have significant comorbid conditions. There are many benefits to tracheostomy followed by delayed reconstruction including larger airway for ease of surgery, graft availability, and reduced effect of postoperative edema. However, long-term tracheostomy is associated with delays in speech and language development that may be reduced with earlier intervention [30]. Figure 26.9 shows typical appearances of a subglottis that is healing well after LTR before (a) and after (b) graft mucosalization.

(d) *Cricotracheal Resection (CTR)*

This procedure also begins through a midline neck incision, but rather than incising and grafting open the stenotic portion of the airway, the stenotic portion is excised. This is only performed if LTR has already been performed and failed, or the stenotic segment is too severely destabilized for LTR to be successful. CTR, by definition, is treatment for subglottic stenosis with or without high tracheal stenosis. The posterior segment of the cricoid cartilage is left in place, but dissection is much more extensive laterally than is required for LTR. This increases the risk of injury to the recurrent laryngeal nerves [31].

(e) *Slide Tracheoplasty*

Slide tracheoplasty is the preferred reconstructive technique for tracheal stenosis, especially when it is a long segment

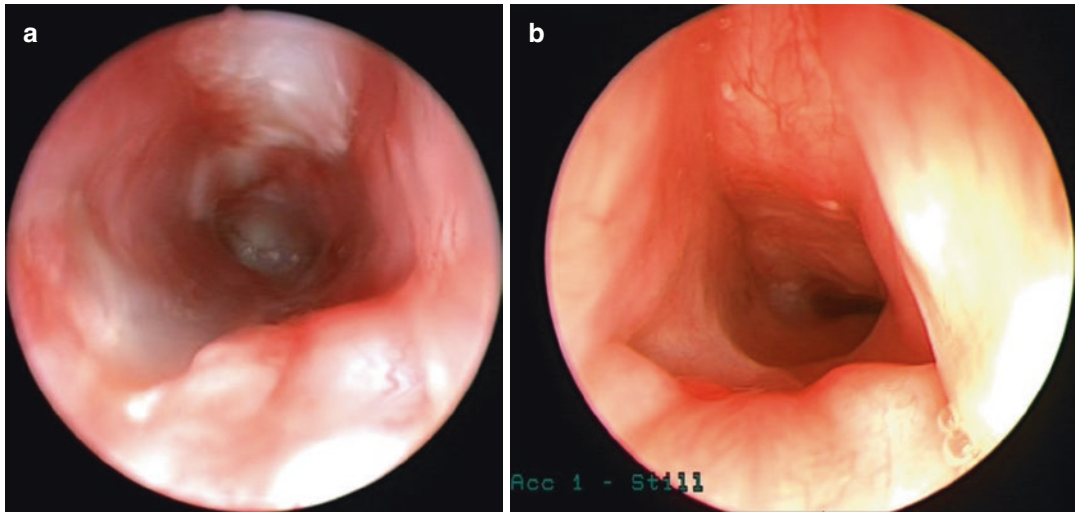

Fig. 26.9 Typical appearance of the subglottis after laryngotracheal reconstruction. (**a**) Anterior and posterior cartilage grafts prior to their mucosalization. (**b**) Anterior and posterior cartilage grafts covered by mucosa

that cannot be resected. It can be performed through a cervical incision or may require midline thoracotomy depending on the level of the stenosis. The stenotic area is incised along its length and in the middle of the stenosis, creating superior and inferior stenotic segments. These segments are then sutured back together in such a way that shortens the length incised while widening its diameter [10]. The trachea develops some degree of figure-of-eight shape due to the suturing technique. The prominence of this appearance is reduced with time. Figure 26.10 shows a well-healing trachea with mild figure-of-eight appearance.

(f) *Tracheal Resection*

Tracheal resection is used when an area of tracheal stenosis is too destabilized for slide tracheoplasty to be successful. Traditionally, it involved end-to-end anastomosis of the airway on either end of the resected trachea, similar to cricotracheal resection. Now, it is more commonly performed in combination with slide tracheoplasty. Whenever a portion of the airway is resected, it is important to perform a tension-free anastomosis which requires release of the airway above and below the resection. Common releases to decrease tension include suprahyoid and infrahyoid, which require release of muscular attachments to the hyoid bone and can cause dysphagia. Tracheal release requires circumferential dissection and places the blood supply to the trachea and the recurrent laryngeal nerves at risk of injury. Pulmonary ligament release can be performed by thoracic surgery.

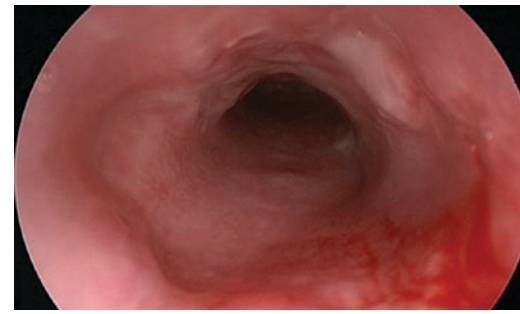

Fig. 26.10 Typical appearance of the airway after slide tracheoplasty. Note the figure-of-eight appearance due to inward collapse at the suture line relative to the lateral-most aspects of the trachea

Future Directions

New research and innovation from multiple disciplines offers hope for improved outcomes and decreased morbidity with respect to laryngotracheal stenosis. From the realm of biomedical engineering, there is research being done to engineer grafts from patient's cells, which would obviate the need for harvesting rib cartilage, reducing perioperative morbidity. There is also research into complete laryngeal transplant [32]. At the molecular level, there is work being done to better elucidate the scar-forming process with the hope to alter cell signaling and prevent acquired stenosis from developing [33].

Increased use of simulation to plan and prepare for surgery holds promise for improved surgical skill of surgeons at the beginning of their career and decreased operative times [34].

Additionally, as the healthcare field continues to focus on patient-centered outcomes, the emphasis on posttreatment voice, feeding, and quality-of-life outcomes has increased. This has resulted in new research quantifying these outcomes with the goal of elucidating drivers of better voice, feeding, and quality-of-life outcomes, which allows for better family counseling and ultimately improved results [35].

References

1. Flint P. Cummings otolaryngology: head and neck surgery. 5th ed: Mosby Elsevier; 2010.
2. Artunc UB, Pala HG, Nese N, Tarhan S, Baytur Y. Prenatal diagnosis of congenital high airway obstruction syndrome: report of two cases and brief review of the literature. Case Rep Obstet Gynecol. 2013;2013:728974.
3. Zur KZ, Wood RE, Elluru RG. Pediatric postcricoid vascular malformation: a diagnostic and treatment challenge. Int J Pediatrc Otorhinolaryngol. 2005;69:1697–701.
4. Suzumura H, Nitta A, Tanaka G, Kuwashima S, Hirabayashi H. Role of infection in the development of acquired subglottic stenosis in neonates with prolonged intubation. Pediatr Int. 2000;42(5):508–13.
5. Duynstee ML, de Krijer RR, Monnier P, Verwoerd CD, Verwoerd-Verhoef HL. Subglottic stenosis after endolaryngeal intubation in infants and children: result of wound healing processes. Int J Pediatr Otorhinolaryngol. 2002;62(1):1–9.
6. Walner D, Loewen MS, Kimura RE. Neonatal subglottic stenosis – incidence and trends. Laryngoscope. 2001;111(1):48–51.
7. Manica D, Schweiger C, Marostica PJ, Kuhl G, Carvalho PR. Association between length of intubation and subglottic stenosis in children. Laryngoscope. 2013;123(4):1049–54.
8. Da Silva OP. Factors influencing acquired upper airway obstruction in newborn infants receiving assisted ventilation because of respiratory failure: an overview. J Perinatol. 1996;16(4):272–5.
9. Herrera P, Caldarone C, Forte V. The current state of congenital tracheal stenosis. Pediatr Surg Int. 2007;23:1033–44.
10. Manning PB, Rutter MJ, Lisec A, Gupta R, Marino BS. One slide fits all: the versatility of slide tracheoplasty with cardiopulmonary bypass support for airway reconstruction in children. J Thorac Cardiovasc Surg. 2011;141:155–61.
11. Buttler CR, Speggiorin S, Rijnberg FM, Roebuck DJ, Muthialu N, Hewitt RJ, Elliott MJ. Outcomes of slide tracheoplasty in 101 children: a 17-year single-center experience. J Thorac Cardiovasc Surg. 2014;147(6):1783–90.
12. Speggiorin S, Torre M, Roebuck DJ, et al. A new morphological classification of congenital tracheobronchial stenosis. Ann Thorac Surg. 2012;93:958–61.
13. Hockstein NG, McDonald-McGinn D, Zackai E, Bartlett S, Huff DS, Jacobs IN. Tracheal anomalies in Pfeiffer syndrome. Arch Otolaryngol Head Neck Surg. 2004;130(11):1298–302.
14. Noorily MR, Farmer DL, Belenky WM, Philippart AI. Congenital tracheal anomalies in the craniosynostosis syndromes. J Pediatr Surg. 1999;34(6):1036–9.
15. Lertsburapa K, Schroeder JW Jr, Sullivan C. Tracheal cartilaginous sleeve in patients with craniosynostosis syndrome: a meta-analysis. J Pediatr Surg. 2010;45:1438–44.
16. Rutter MJ, Vijayasekaran S, Salamone FN, et al. Deficient tracheal rings. Int J Pediatr Otorhinolaryngol. 2006;70:1981–4.
17. Myer CM 3rd, O'Connor DM, Cotton RT. Proposed grading system for subglottic stenosis based on endotracheal tube sizes. Ann Otol Rhinol Laryngol. 1994;103(1):319–23.
18. Collaco JM, Aherrera AD, Au Yeung KJ, Lefton-Greif MA, Hoch J, Skinner ML. Interdisciplinary pediatric aerodigestive care and reduction in health care costs and burden. JAMA Otolaryngol Head Neck Surg. 2015;141(2):101–5.
19. Kocyildirim E, Kanani M, Roebuck D, et al. Long-segment tracheal stenosis: slide tracheoplasty and a multidisciplinary approach improve outcomes and reduce costs. J Thorac Cardiovasc Surg. 2004;128:876–82.
20. Boesch RP, Balakrishnan K, Acra S, et al. Structure and functions of pediatric aerodigestive programs: a consensus statement. Pediatrics. 2018;141(3)

21. Piccione J, Boesch RP. The multidisciplinary approach to pediatric aerodigestive disorders. Curr Probl Pediatr Adolesc Health Care. 2018;48(3):66–70.
22. Roh JL, Lee YW, Park HT. Effect of acid, pepsin, and bile acid on the stenotic progression of traumatized subglottis. Am J Gatroenterol. 2006;101(6):1186–92.
23. Blumin JH, Johnston N. Evidence of extraesophageal reflux in idiopathic subglottic stenosis. Laryngoscope. 2011;121(6):1266–73.
24. Ehsan Z, Mahmoud M, Shott SR, Amin RS, Ishman SL. The effects of anesthesia and opioids on the upper airway: a systematic review. Laryngoscope. 2016;126(1):270–84.
25. Vazquez Garcia G, Giordano T, Moran K, Jacobs IN, Piccione J. The role of flexible bronchoscopy and bronchoalveolar lavage as part of the pre-operative evaluation for laryngotracheal reconstruction. Am J Respir Crit Care Med. 2017;195:A4118.
26. Cheung K, Chadha NK. Primary dilation as a treatment for laryngotracheal stenosis: a systematic review. Int J Pediatr Otorhinolaryngol. 2013;77(5):623–8.
27. Lang M, Brietzke SE. A systematic review and meta-analysis of endoscopic balloon dilation of pediatric subglottic stenosis. Otolaryngol Head Neck Surg. 2014;150(2):174–9.
28. Rutter MJ, Hart CK, deAlarcon A, Daniel SJ, Parikh SR, Balakrishnan K, Lam D, Johnson K, Sidell DR. Endoscopic anterior-posterior cricoid split for pediatric bilateral vocal cord paralysis. Laryngoscope. 2018;128(1):257–63.
29. White DR, Bravo M, Vijayasekaran S, Rutter MJ, Cotton RT, Elluru RG. Laryngotracheoplasty as an alternative to tracheostomy in infants younger than six months. Arch Otolaryngol Head Neck Surg. 2009;135(5):445–7.
30. Jiang D, Morrison GA. The influence of long-term tracheostomy on speech and language development in children. Int J Pediatr Otorhinolaryngol. 2003;67 supp 1:S17–20.
31. Hartley BE, Cotton RT. Paediatric airway stenosis: laryngotracheal reconstruction or cricotracheal resection? Clin Otolaryngol Allied Sci. 2000;25(5):342–9.
32. Morrison RJ, Nasser NB, Kashlan KN, Zopf DA, Milner DJ, Flanagan CL, Wheeler MB, Green GE, Hollister SJ. Co-culture of adipose derived stem cells and chrondrocytes on three-dimensionally printed bioscaffolds for craniofacial cartilage engineering. Laryngscope. 2018;128:E251–57.
33. Motz KM, Yin LX, Samad I, Ding D, Murphy MK, Duvvuri M, et al. Quantification of inflammatory markers in laryngotracheal stenosis. Otolaryngol Head Neck Surg. 2017;157(3):466–72.
34. Ha JF, Morrison RJ, Green GE, Zopf DA. Computer-aided design and 3-dimensional printing for costal cartilage simulation of airway graft carving. Otolaryngol Head Neck Surg. 2017;156(6):1044–7.
35. Pullens B, Dulfer K, Buysse CMP, Hoeve LJ, Timmerman MK, Joosten KFM. Long-term quality of life in children after open airway surgery for laryngotracheal stenosis. Int J Pediatr Otorhinolaryngol. 2016;84:88–93.

Airway Tumors

27

Claudia Mattos, Brandy Johnson, and Joseph Piccione

Introduction

Primary pediatric airway tumors are very rare, and the majority of them are malignant (62%) [1, 2]. The inflammatory myofibroblastic tumor is the most common benign lung tumor in the pediatric population, while the carcinoid tumor is the most common malignant endobronchial tumor in older children and adolescents [2–4]. According to Pio et al., the median age at diagnosis is 10 years and younger children have worse outcomes in terms of disease progression and mortality, although overall survival prognosis is excellent (>90%) in comparison with other pediatric malignancies [2]. It is difficult to diagnose primary airway tumors in children because symptoms are often nonspecific and can mimic other more common diagnoses [1]. For this reason, airway tumors should be considered in the case of recurrent respiratory symptoms. Bronchoscopy can be used to diagnose suspected airway masses or tumors; flexible is better for distal airway lesions and rigid is better for laryngeal and tracheal lesions [5]. Flexible bronchoscopy can also be used for diagnosis of "pseudotumors" in the lung such as fungal infections and pulmonary TB in children [6].

Types of Airway Tumors

Malignant

Carcinoid Tumors

Airway carcinoid tumors are the most common primary pulmonary neoplasm in the pediatric population. In a multicenter international retrospective study, Pio et el. examined 78 children (<18 years of age) who had been diagnosed with a primary tracheobronchial tumor from 2000 to 2015. Of these 78 children, 31 (40%) were identified to have bronchial carcinoid tumor [2]. There is apparently no significant difference in distribution between males and females and one study found that the average age at diagnosis was 17 years [7] (Fig. 27.1).

Electronic Supplementary Material: The online version of this chapter (https://doi.org/10.1007/978-3-030-54924-4_27) contains supplementary material, which is available to authorized users.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_27

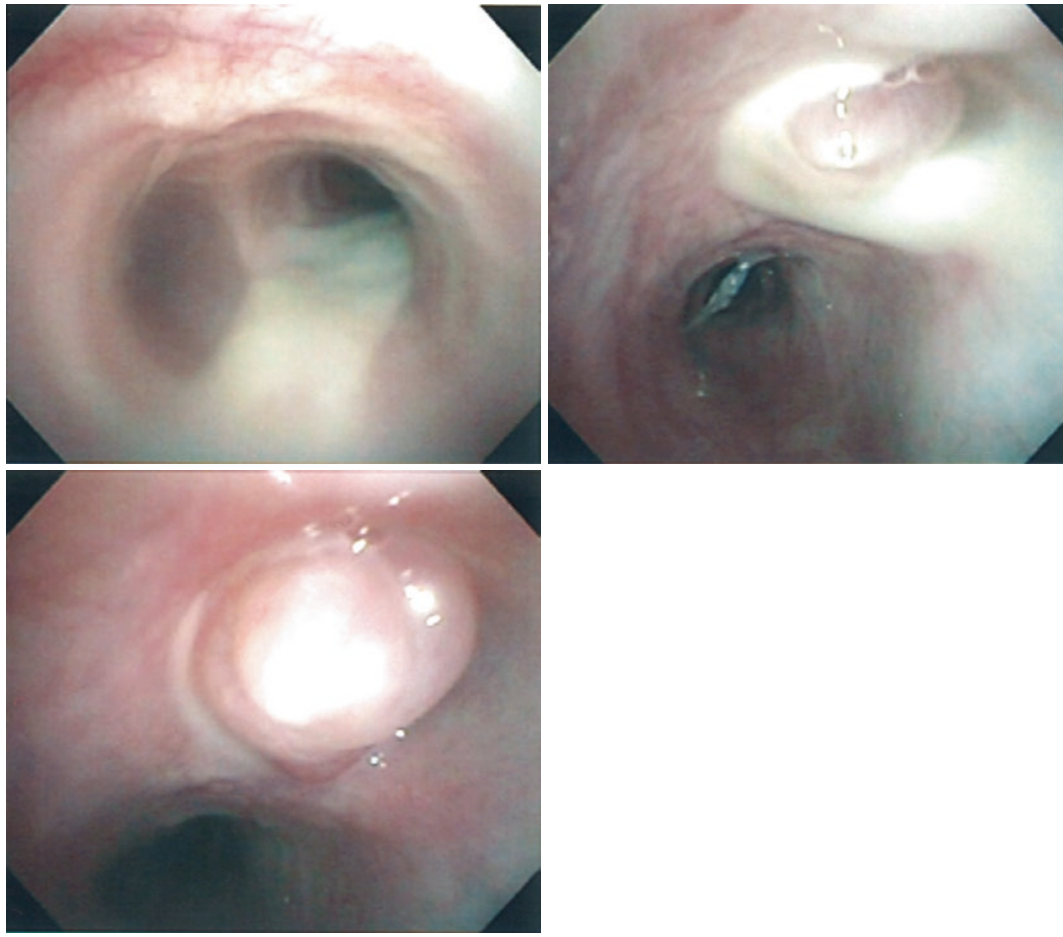

Fig. 27.1 Carcinoid tumor

Carcinoid tumors are thought to arise from the neuroendocrine argentaffin cells of the epithelial component from the bronchial mucosa known as the Kulchitsky cell [7]. About 75% arise in the lobar bronchi, 10% in the mainstem bronchi, and 15% in the lung periphery [1]. The reported rate of metastasis at the time of diagnosis is 5–27%. However, the tendency for metastasis depends on the histologic appearance of the tumor; the more atypical the histology, the greater the likelihood for metastasis [7].

The most common presenting symptoms include cough, hemoptysis, and pneumonitis. Pediatric patients are also more likely to experience wheezing and atelectasis, in contrast to adults. In a sample of 17 children (<21) from Massachusetts General Hospital, no patient diagnosed with a carcinoid airway tumor was found to be asymptomatic. Pediatric airway carcinoid tumors also rarely result in carcinoid syndrome, with a reported 1–7% incidence [7]. The most frequent abnormality seen on imaging was a mass associated with segmental or lobar collapse [1]. Symptom-free recovery can be achieved in the majority of cases with surgical resection [7].

Mucoepidermoid Carcinomas

Mucoepidermoid carcinomas are rare tumors that represent 0.1–0.2% of primary lung tumors. They typically arise from bronchial mucous glands and account for 25–70% of all bronchial tumors in children [2, 4, 8]. They usually present in children with a mean and median age of 10 years and are most commonly found in the mainstem bronchi or proximal lobar bronchi. There does not appear to be a significant gender predominance

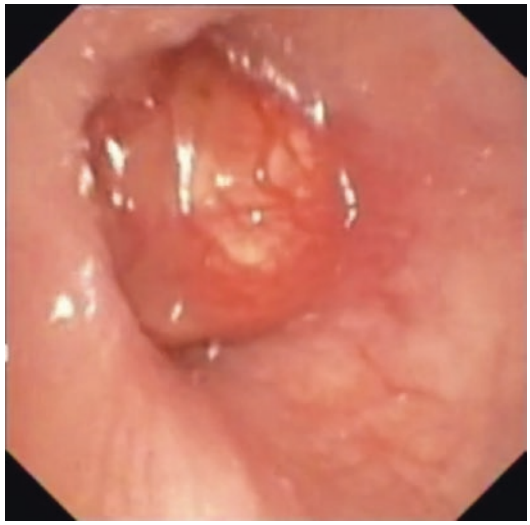

Fig. 27.2 Mucoepidermoid carcinoma

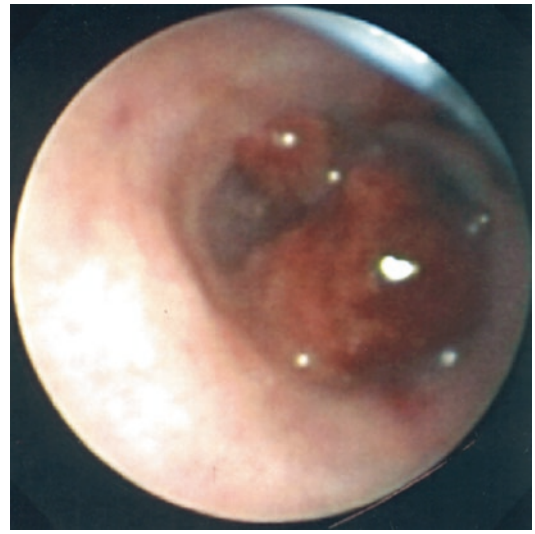

Fig. 27.3 Inflammatory myofibroblastic tumor (trachea)

[9, 10]. Common presenting symptoms include cough, productive sputum, fever, or obstruction symptoms [8] (Fig. 27.2).

Mucoepidermoid lesions are typically exophytic masses containing a combination of mucus-secreting cells, epidermoid cells, and intermediate cells covered by normal respiratory epithelium and tumors are typically slow growing and locally invasive, but the prognosis is good and there is low metastatic potential [1, 8–10]. It has been shown that approximately 80% of bronchial mucoepidermoid carcinomas have a CRTC1–MAML2 fusion protein formed by a translocation mutation of chromosome (11, 19) and it appears that tumors containing this mutation have a favorable prognosis [8].

Fibrosarcoma

Primary bronchopulmonary fibrosarcomas are uncommon in children (9.6% of primary bronchopulmonary malignant tumors), but they tend to be of low grade, particularly when they are endobronchial [11]. Endobronchial fibrosarcomas are more commonly seen in children, while intrapulmonary fibrosarcomas are typically seen in adults and the elderly [12]. There does not seem to be a predominance for males or females. Most fibrosarcomas of the airway arise in the primary bronchus or distally and would be unusual to be found in the trachea [13]. These low-grade tumors have a higher rate of local recurrence than that of metastasizing [13]. Histologically, they are densely packed spindle-cell tumors with scattered lymphocytes and must be differentiated from other spindle-cell tumors such as plasma cell granuloma, leiomyosarcoma, fibromatosis, fibrous histiocytoma, malignant melanoma, and spindle-cell carcinoma [11, 13].

Benign

Inflammatory Myofibroblastic Tumor (aka Plasma Cell Granuloma)

Inflammatory myofibroblastic tumors (IMTs), previously known as plasma cell granulomas, are the most common benign lung tumors in children (52.2% of cases of benign tumors), and most commonly occur in young adults and adolescents [11, 14, 15]. Of the 78 children examined by Pio et al., 19 (25%) were identified to have an inflammatory myofibroblastic tumor [2]. They are commonly seen in the lungs but rarely in the airways. Few cases have been reported of IMTs in the airway, specifically in the larynx or trachea, and they typically present with respiratory and obstructive symptoms [16, 17]. There does not appear to be a significant male or female predominance associated with IMTs [2] (Fig. 27.3).

IMTs are slow growing and locally invasive and are thought to represent an inflammatory response to prior infectious or traumatic insult [1]. They can be associated with multiple recurrences and there are only a few reported cases of metastasis [14, 18]. IMTs are composed of lymphocytes, histiocytes, macrophages, foam cells, and plasma cells within a spindle-shaped stroma [14].

The etiology of IMT remains uncertain, but RNA hybridization in situ has linked IMT to Epstein–Barr virus [18]. Some possible predisposing factors include preceding infection/inflammation, radiotherapy, and local trauma [14]. Immunohistochemical staining can also be useful in diagnosing IMT. Specifically, vimentin has been found to be positive in 89–99% of cases, smooth muscle actin in 92%, and muscle-specific actin in 89% [18].

Hamartomas

Hamartomas are the second most common benign pulmonary neoplasm, making up about 23.9% of cases of benign lesions [15]. They are developmental anomalies made up of focal excessive growth of native tissue in excess and that does not resemble the normal tissue architecture. There are 2 categories of hamartomas: mesenchymal hamartomas (most common) and epithelial or glandular hamartomas. Hamartomas can occur anywhere but are frequently seen in the lungs or abdominal cavity [19]. Anywhere from approximately 1.5% to 20% of pulmonary hamartomas are endobronchial rather than parenchymal [20].

Airway hamartomas usually have a lot of cartilage and glandular tissue. Histologically, they typically present with normal respiratory epithelium with scant capillary vessels, primitive cartilage, and no mucous glands. They can be due to a developmental abnormality rather than a neoplasm or due to previous trauma to the airway. Although these tumors tend to be asymptomatic and do not need to be removed in adults, both peripheral and centrally located hamartomas can lead to significant symptoms in children, and surgical removal is required [21]. Hamartomas are benign growths and do not have a propensity to metastasize [19].

Mucus Gland Adenoma

Mucus gland adenomas are benign tumors that arise from the mucous-secreting glands of the larger airway mucosa. They are usually seen in the bronchus but also seen in the trachea or peripheral airways [22]. One study found that mucus gland adenomas are 3.3% of benign primary pulmonary neoplasms in children [15]. They are seen in children of all ages and there is no male or female predilection. Histologically, they are composed of large vacuolated cells with oval nuclei displaced to the periphery. They can present with nonspecific symptoms including cough, wheezing, hemoptysis, recurrent pneumonia, emphysema, asthma, and atelectasis [22]. Although benign, even when completely removed, they have potential for local recurrence [23].

Hemangioma

A hemangioma is a vascular tumor—made up of structural malformations of the vasculature. Hemangiomas are more common in female infants (3× as likely as male infants), and there is an increased incidence in premature infants [24]. The incidence of hemangiomas on the head and neck is 4–5% in the general population [25]. Cutaneous hemangioma lesions are associated with airway hemangiomas (50%); so, this, along with noisy breathing in an infant, should prompt assessment of the airway [24]. In the airway, they may be life threatening due to airway obstruction and will typically present by the first or second month of life [24, 26].

Hemangiomas enter a proliferative phase in which the hemangioma grows rapidly, and is then followed by spontaneous regression in later years. Due to the narrow nature of infants' airways, this period of proliferation in a hemangioma located in the airway can cause obstruction [25]. Histologically, infantile hemangiomas will typically stain positive for Glucose transporter 1 (GLUT-1) and this marker can be used to confirm the diagnosis [27].

The most common symptom at presentation is some form of respiratory distress, most commonly inspiratory stridor [28]. Airway hemangiomas are most commonly located in the subglottic region and present with hoarseness and stridor and lesions may result in respiratory failure, usually when the infant is 6–12 weeks old [24, 27]. A hemangioma usually appears as a smooth submucosal mass, situated directly below the vocal cords, most often posteriorly, and frequently unilateral [28]. Symptomatic hemangiomas can be managed medically or can be excised surgically, and, although carry a chance of recurrence, it is uncommon [29].

Pseudotumors of the Airway

Tuberculosis

Pulmonary TB is the most common clinical form of TB in children. Although there is potential for compression of the airways (most commonly the bronchus intermedius, left main bronchus, and trachea), airway involvement is rarely so severe that an intervention is required to relieve airway obstruction [6].

Endobronchial tuberculosis (EBTB) is a tuberculosis infection of the tracheobronchial tree and is present in 10–40% of patients with active pulmonary tuberculosis. EBTB is more common in young adults, more than half of cases seen at less than 35 years of age, and exhibits a female predominance. The typical bronchoscopic finding is white gelatinous granulation tissue with a mucosa that is red, nodular, vascular, and sometimes ulcerated. Nucleic acid amplification tests may help with rapid detection of *Mycobacterium tuberculosis*. Sputum samples and chest X-rays may also be helpful in diagnosis [30]. Nontuberculous mycobacterial infections can also be associated with endobronchial masses, particularly in immunocompromised children.

Coccidioidomycosis

Coccidioides immitis is endemic in Southern California and spores are present in the soil. Inhalation of the dust contaminated with spores may result in infection. Coccidiomycosis can be mistaken for a malignant tumor on imaging but confirmed to be a fungal infection when biopsied and cultured [31].

Endotracheal and endobronchial diseases are rare. In a study of 38 case reports of patients aged 0.4 years–54 years with coccidioidomycosis, 17 cases had involvement of the bronchi and 5 had involvement of the trachea. In 32 cases, there was involvement of the lung parenchyma. Of the 38 cases, 23 were male and 6 were female, and in 9 cases, the sex was not reported [32]. Examination of the infected tissue will show noncaseating granulomatous inflammation [31].

Actinomyces

Pediatric actinomycosis infections are uncommon and even more rare in children under the age of 5. In adults, actinomycosis occurs 3 times as often in males than in females. In children, however, Golden et al. observes that this predilection may be less prominent in children (Fig. 27.4).

Actinomyces israelii is the most common cause of actinomycosis in children. *A. israelii* is a normal commensal organism of the mouth and tonsillar crypts and may become invasive. Trauma to the mouth and dental caries can predispose the organism to become invasive, particularly in immunocompromised patients. Thoracic infection is thought to be due to inhalation of infected secretions. In a study of patients with actinomycosis of all ages, it was found that 15% had thoracic involvement, with the primary lesion being in the bronchioles. Sulfur granules on biopsy are

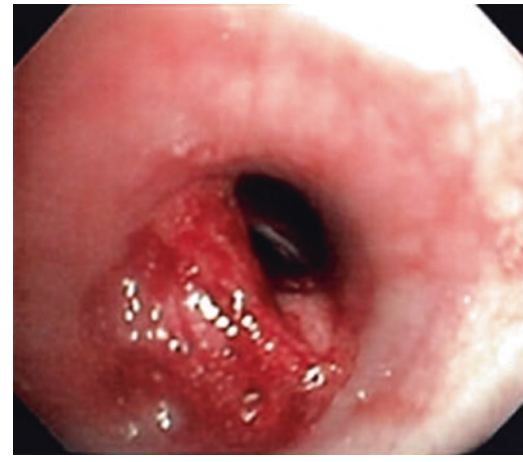

Fig. 27.4 Actinomyces pseudotumor

suggestive of actinomycosis and infection can be confirmed by Gram stain of the Gram-positive branching filaments [33, 34].

The Role of Flexible Bronchoscopy in Diagnosis and Management of Pediatric Airway Tumors

While the gross appearance of airway tumors varies between different tumor types, it is rarely possible to confirm the diagnosis based solely on appearance. Likewise, tumor location can be useful in weighting the probability of one tumor type over another but is rarely definitive. Most tumors will have a well-mucosalized surface that may or may not appear visibly inflamed. They do have a greater tendency to bleed than the surrounding healthy mucosa, but clinically significant bleeding from the mucosa itself is rare. It is also prone to developing edema following direct contact with the bronchoscope, so careful gentle exploration is important.

At the time of clinical presentation, most children with airway tumors have post-obstructive bronchitis or pneumonia. When feasible, in children without complete tracheobronchial obstruction, treating with antibiotics beginning several days prior to bronchoscopy can improve the tolerability of the procedure. In either case, passing the bronchoscope alongside the mass is useful for obtaining specimens for culture, understanding the full extent of bronchial obstruction and assessing for evidence of bronchiectasis. It is also important to assess whether the tumor is pedunculated or originates from a stalk. This information is useful in narrowing the differential diagnosis and determining the best management strategy.

Endobronchial biopsy of airway tumors offers several clear benefits. When adequate tissue samples are obtained, the diagnosis can be confirmed and prognostic indicators can be assessed. With advances in cancer genomic analysis, this information can also provide guidance regarding whether chemotherapy is indicated and whether targeted chemotherapeutics are available for specific mutations within the tumor. It can also differentiate between true tumors and infectious pseudotumors, which require distinctly different therapies. Certain tumor types (IMT, infectious pseudotumors) can be effectively removed endoscopically (Fig. 27.5), while others generally require complete open surgical resection with verification of clean margins (mucoepidermoid carcinoma, most carcinoids). Since most airway tumors are located beyond the mucosal surface, it is often necessary to repeatedly biopsy the same location to insure submucosal and deeper tissue samples are obtained. Intraoperative light microscopy of frozen tissue sections rarely provides a

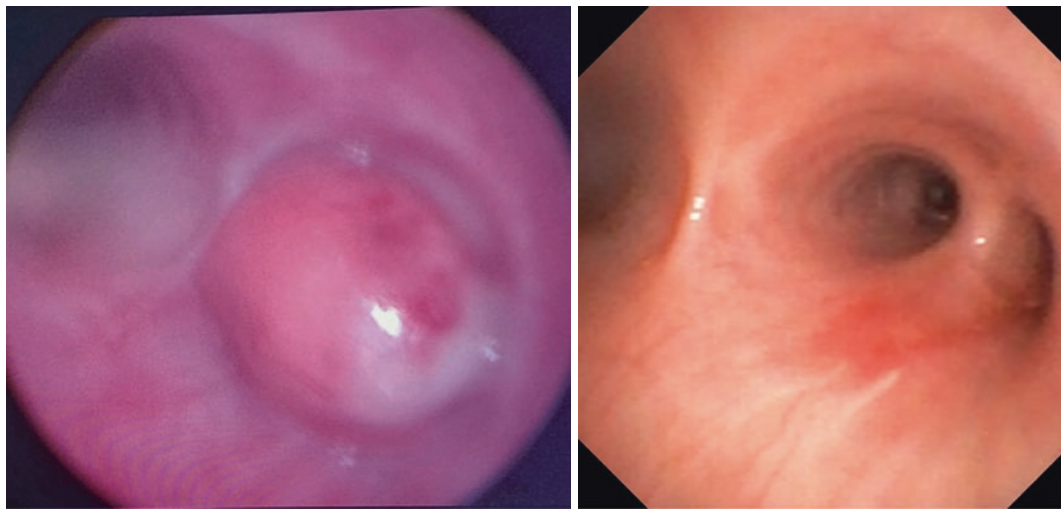

Fig. 27.5 Inflammatory myofibroblastic tumor before and after endoscopic resection

definitive diagnosis but can provide guidance regarding adequacy of the biopsy and whether additional specimens are needed.

There are risks to endobronchial biopsy and due caution must be observed; however, it can be performed safely in the vast majority of cases provided there are appropriate tools and an adequately trained and experienced multidisciplinary team is present or readily available to assist. The most commonly encountered complication is bleeding. The risk of significant bleeding can be mitigated by administering topical oxymetazoline or epinephrine prior to biopsy. If blood vessels are visible on the surface of the tumor, they should be avoided or cauterized prior to biopsy. Endobronchial forceps typically provide adequate tumor sampling and the largest forceps that can be passed through the working channel of the selected bronchoscope are generally preferred. Cryobiopsy may allow for larger specimens but carries a higher risk of bleeding. In the event of persistent bleeding, topical agents can be reapplied and, in rare circumstances, selective mainstem endotracheal intubation with a cuffed endotracheal tube may be required to protect and ventilate the unaffected lung until the bleeding is controlled. The other major risks of endobronchial biopsy are pneumothorax and pneumomediastinum. Although uncommon, it is important to be alert to signs of intrathoracic air leak and consider chest radiograph following the biopsy.

After a diagnosis has been established and staging rendered, various therapeutic options are then considered in designing the ideal approach to treatment or palliation. Tumor pathology, size, and location, as well as patient comorbidities, serve as guides to determining the most appropriate intervention. Chemotherapy, radiation therapy, immunotherapy, and surgical excision exist as the mainstays of treatment for airway and lung neoplasms; however, there are also a variety of bronchoscopic techniques available for local treatment. These modalities offer minimally invasive interventions which achieve rapid results. The same guiding principles and patient risk factors are employed to determine the most appropriate endobronchial approach. Practitioners should consider devising treatment regimens in collaboration with multidisciplinary teams, comprised of surgical and oncology experts.

Both rigid bronchoscopy and flexible bronchoscopy can be implemented, with the use of adjunct tools, in the investigation into these described airway lesions and addressing their associated symptomatology. Indications for bronchoscopic intervention include alleviation of chest pain and dyspnea, central airway obstruction, bleeding, tissue resection, post-obstructive tissue collapse, or infection. Previously applied as palliative measures, in cases of advanced endobronchial malignancy, improvements in technology now allow for bronchoscopy to aid in the early detection and treatment of cancers [35]. Each approach has its own inherent benefits; however, general characteristics of the rigid bronchoscope confine its application to centrally located lesions, whereas the flexible bronchoscope permits access to more distal tumors. Regardless of intentions to pursue treatment with one particular scope, it is customary to have both, along with the respective operator(s), available during a case should intraoperative findings differ from the pathology anticipated. For example, should difficulty with ventilation be encountered, rigid bronchoscopes allow for improved control of the airway and larger working channels for manipulation of instruments and tissue.

There are a variety of instruments used in conjunction with the bronchoscope, and some of the more useful tools used to address airway tumors include endobronchial ultrasound (EBUS), photodynamic therapy, electrocautery, cryotherapy, radiofrequency ablation, and airway endoprostheses for stenting. Local tissue invasion and assessment of nearby structures can be evaluated via EBUS and tissue removal can then be facilitated by laser, electrocautery, and cryotherapy when deemed appropriate. EBUS also allows for biopsy of suspicious lymph nodes to assist in staging efforts. Moreover, bronchoscopic intervention should be limited to strictly endoluminal tumors, highlighting the importance of characterizing local tissue whether EBUS or other advanced imaging techniques are utilized [36]. Mechanical, thermal, and chemical debulking can be exe-

cuted with a variety of specialized devices, such as snare electrocautery in cases of hamartomas removal or intra-tumoral chemotherapy for susceptible malignancies.

Risks of these therapeutic procedures are viewed as relatively minimal and considered to be outweighed by the potential benefits. In cases in which normal lung tissue can be spared and open thoracic surgery is circumvented, one could imagine that bronchoscopy would be preferred. Nonoperative candidates benefit from the alternate treatment options, whether curative or palliative. Despite the myriad of benefits associated with these bronchoscopic techniques, risks reviewed with families prior to the procedure are similar to those as detailed above and may have serious consequences.

References

1. McCahon E. Lung tumours in children. Paediatr Respir Rev. 2006;7(3):191–6.
2. Pio L, Varela P, Eliott MJ, et al. Pediatric airway tumors: a report from the International Network of Pediatric Airway Teams (INPAT). Laryngoscope. 2020;130(4):E243–51.
3. Dishop MK, Kuruvilla S. Primary and metastatic lung tumors in the pediatric population: a review and 25-year experience at a large children's hospital. Arch Pathol Lab Med. 2008;132(7):1079–103.
4. Al-Qahtani AR, Di Lorenzo M, Yazbeck S. Endobronchial tumors in children: institutional experience and literature review. J Pediatr Surg. 2003;38(5):733–6.
5. Soyer T. The role bronchoscopy in the diagnosis of airway disease in children. J Thorac Dis. 2016;8(11):3420–6.
6. Goussard P. The role of bronchoscopy in the diagnosis and management of pediatric pulmonary tuberculosis. Expert Rev Respir Med. 2014;8(1):101–9.
7. Wang LT, Wilkins EW, Bode HH. Bronchial carcinoid tumors in pediatric patients. Chest. 1993;103(5):1426–8.
8. Wang H, Zhang J, Li D, Zhang N, Li J, Mao J. Efficacy of Bronchoscopic therapies for bronchial Mucoepidermoid carcinoma in children: results from six patients. Tumori J. 2015;101(1):52–6.
9. Jaramillo S, Rojas Y, Slater BJ, et al. Childhood and adolescent tracheobronchial mucoepidermoid carcinoma (MEC): a case-series and review of the literature. Pediatr Surg Int. 2016;32(4):417–24.
10. Dinopoulos A, Lagona E, Stinios I, Konstadinidou A, Kattamis C. Mucoepidermoid carcinoma of the bronchus. Pediatr Hematol Oncol. 2000;17(5):401–8.
11. Savas C, Candir O, Ozguner F. Acute respiratory distress due to fibrosarcoma of the carina in a child. Pediatr Pulmonol. 2004;38(4):355–7.
12. Gupta A, Marsh R, Jordan S, et al. Endobronchial fibrosarcoma presenting as recurrent left-sided pneumonia. Pediatr Pulmonol. 2011;46(6):610–3.
13. Shiraishi T, Kawahara K, Shirakusa T, et al. Primary tracheal fibrosarcoma in a child: a case of tracheal resection under ECMO support. Thorac Cardiovasc Surg. 1997;45(5):252–4.
14. Breen DP. A rare cause of an endobronchial tumour in children: the role of interventional bronchoscopy in the diagnosis and treatment of tumours while preserving anatomy and lung function. Respiration. 2008;76(4):444–8.
15. Hancock BJ, Di Lorenzo M, Youssef S, Yazbeck S, Marcotte JE, Collin PP. Childhood primary pulmonary neoplasms. J Pediatr Surg. 1993;28(9):1133–6.
16. Coffin CM, Watterson J, Priest JR, Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases. Am J Surg Pathol. 1995;19(8):859–72.
17. Karnak I, Haliloglu M, Orhan D, Yalcin B, Kalayci O. Pure endobronchial inflammatory myofibroblastic tumor in children. J Pediatr Hematol Oncol. 2014;36(2):108–10.
18. Rodrigues M, Taylor RJ, Sun CC, Wolf JS. Inflammatory myofibroblastic tumor of the larynx in a 2-year-old male. ORL J Otorhinolaryngol Relat Spec. 2005;67(2):101–5.
19. Kslal FM, Acar M, Acar B, Karahan F. Laryngeal fibrous hamartoma presenting with airway obstruction at birth. J Craniofac Surg. 2013;24(4):e383–4.
20. Roby BB, Drehner D, Sidman JD. Pediatric tracheal and endobronchial tumors: an institutional experience. Arch Otolaryngol Head Neck Surg. 2011;137(9):925–9.
21. Ibrahim A, Raja R. Endobronchial chondromatous hamartoma in an infant. Pediatr Pulmonol. 2003;35(1):67–9.
22. Peres LC, Castro ECDC. Mucous gland adenoma of the bronchus in a 5-year-old child: case report and review of the literature. Jornal Brasileiro de Patologia e Medicina Laboratorial. 2003;39:365–9.
23. Morini F, Quattrucci S, Cozzi DA, et al. Bronchial adenoma: an unusual cause of recurrent pneumonia in childhood. Ann Thorac Surg. 2003;76(6):2085–7.
24. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. N Engl J Med. 1999;341(3):173–81.
25. McCormick AA, Tarchichi T, Azbell C, Grunwaldt L, Jabbour N. Subglottic hemangioma: understanding the association with facial segmental hemangioma in a beard distribution. Int J Pediatr Otorhinolaryngol. 2018;113:34–7.
26. Onder SS, Gergin O, Karabulut B. A life threatening subglottic and mediastinal hemangioma in an infant. J Craniofac Surg. 2019;30(5):e402–4.
27. Mackey WS. Infantile hemangioma with a focus on airway hemangioma. ORL Head Neck Nurs. 2016;34(2):18–23.

28. Shikhani AH. Infantile subglottic hemangiomas. An update. A Otol Rhinol Laryngol. 1986;95(4):336–47.
29. Darrow DH. Management of infantile hemangiomas of the airway. Otolaryngol Clin N Am. 2018;51(1):133–46.
30. Kashyap S, Mohapatra PR, Saini V. Endobronchial tuberculosis. Indian J Chest Dis Allied Sci. 2003;45(4):247–56.
31. Winter B, Villaveces J, Spector M. Coccidioidomycosis accompanied by acute tracheal obstruction in a child. JAMA. 1966;195(12):1001–4.
32. Polesky A, Kirsch CM, Snyder LS, et al. Airway coccidioidomycosis--report of cases and review. Clin Infect Dis. 1999;28(6):1273–80.
33. Golden N, Cohen H, Weissbrot J, Silverman S. Thoracic actinomycosis in childhood. Clin Pediatr (Phila). 1985;24(11):646–50.
34. Han JY, Lee KN, Lee JK, et al. An overview of thoracic actinomycosis: CT features. Insights Imaging. 2013;4(2):245–52.
35. Scarlata S, Fuso L, Lucantoni G, et al. The technique of endoscopic airway tumor treatment. J Thorac Dis. 2017;9(8):2619–39.
36. Guibert N, Mhanna L, Droneau S, et al. Techniques of endoscopic airway tumor treatment. J Thorac Dis. 2016;8(11):3343–60.

Hemoptysis and Pulmonary Hemorrhage

28

Elizabeth K. Fiorino

Definition

Hemoptysis is defined as expectorating blood. Pulmonary hemorrhage is defined as bleeding from the tracheobronchial tree or alveolar environment. Varying volume-related definitions of pulmonary hemorrhage have been proposed, including mild (<150 ml), moderate (150–400 ml), and massive (>400 ml), based on a visual assessment, in a 24 hour period [1, 2]. The usefulness of this definition, however, is limited; others have argued that clinical effect (i.e., respiratory and cardiovascular compromise) determines the significance of a bleed [3].

Epidemiology and Outcome

In children the incidence of pulmonary hemorrhage is difficult to define. Most cases of true hemoptysis in children occur in those with a history of congenital heart disease or bronchiectasis, usually due to an underlying condition such as cystic fibrosis or immune deficiency [2, 4]. Pneumonia and infection comprise the next most common cause. In a recent study of hemoptysis in patients without congenital heart disease or cystic fibrosis, the leading etiologies were infection, neoplasm, and a collection of rare disorders. Those with malignancy and other illnesses had the highest mortality [5]. Welsh and others evaluated pulmonary hemorrhage specifically in infants, in which the leading diagnosis was congenital heart disease, followed by prematurity, lung disease, and coagulopathies. Nonaccidental trauma without accompanying retinal hemorrhage or fracture occurred in 3 patients. The authors concluded that pulmonary hemorrhage in infants is a rare occurrence, with 157 infants presenting with pulmonary hemorrhage over 10 years [6].

Anatomy and Pathophysiology

Pulmonary hemorrhage may arise from different areas of the tracheobronchial tree. Bleeding may come from the bronchial circulation, which supplies the airways and originates from the systemic circulation, from the aorta or intercostal arteries at T5-6. Though the bronchial circulation contributes only 1% of total blood flow to the lung, bleeding from this system is often of greater volume, due to the higher pressure. Conversely, the bulk of the blood flow to the lung is from the pulmonary circulation, a high volume and low pressure system. There is a high capacitance in this system, and the alveoli may accommodate a large volume of blood without actual hemoptysis.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_28

Bleeds may also arise from a focal lesion, such as an airway tumor, though this is rare in children. Mortality from pulmonary hemorrhage may result from exsanguination, but, more commonly, both morbidity and mortality result from impaired gas exchange. Of note, the presence of 400 ml of blood in the tracheobronchial tree may result in impaired gas exchange.

Differential Diagnosis

The differential diagnosis of pulmonary hemorrhage is broad, and may be approached systematically, with characterization as localized or diffuse; if localized, within parenchyma or conducting airways; and if diffuse, by age [7]. One also needs to consider the presence of a known underlying pulmonary or cardiac condition. In an otherwise healthy child with a cough, the most likely diagnosis is infection. Other etiologies outside the lung include gastrointestinal causes, nasopharyngeal bleeding, and factitious hemoptysis. See Table 28.1 for further elaboration.

In a child with cystic fibrosis (CF) and liver disease, for example, it may be difficult to differentiate hemoptysis from hematemesis due to esophageal varices. With hemoptysis patients will describe a sensation of gurgling in the chest which can localize the site of bleeding with surprising accuracy. Hemoptysis may occur in individuals with CF in the context of an exacerbation, but also due to bronchial artery collaterals. This may be exacerbated by vitamin K deficiency and coagulopathy due to nutritional issues. Bronchial collaterals may be present in cystic fibrosis, in an undiagnosed congenital lung lesion, and in cyanotic congenital heart disease. In addition, these large volume bleeds can occur in hereditary hemorrhagic telangiectasia, due to pulmonary arteriovenous malformations. These bleeds can often be large volume, and must be clarified and diagnosed quickly.

Infections may lead to hemoptysis – bronchitis, pneumonia with or without development of a bronchial artery collateral, or a fungal infection. Especially in a patient who is immunosuppressed or who has severe bronchiectasis, the risk of angioinvasive fungal disease is high. Tuberculosis is a leading cause of hemoptysis in adults worldwide [3]; though more rare in children, it should still be considered, especially in the context of history and location.

Vasculitides and rheumatologic conditions can also present with hemoptysis – either as

Table 28.1 Hemoptysis: differential diagnosis

Pulmonary
Localized
Arteriovenous malformation
Airway tumor
Bronchial adenoma
Carcionoid
Mucoepidermoid carcinoma
Aortopulmonary collateral vessels
Trachobronchial varices
Tracheo-inominate arterial fistula
Bronchiectasis
Cystic fibrosis
Immune deficiency
Primary ciliary dyskinesia
Anatomical abnormality
Duplication cyst
Bronchopulmonary sequestration
Congenital pulmonary airway malformation
Infection
Bacterial pneumonia
Bronchitis/tracheitis
Angioinvasive fungal disease
Mycobacterial disease
Lung abscess
Diffuse
Pulmonary vasculitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis
Systemic lupus erythematosus
Capillaritis
Idiopathic pulmonary hemosiderosis
Diffuse alveolar damage (post stem cell transplant)
Multiple AVM
Pulmonary hypertension
Miscellaneous
Coagulopathy
Foreign body
Catamenial hemoptysis
Trauma
Nonaccidental trauma
Factitious
Gastrointestinal source

initial presentation or as complication. In systemic lupus erythematosus (SLE), for example, pulmonary hemorrhage early in the course is associated with increased mortality [8]. The ANCA- associated vasculitides include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis. In these cases, there may be associated extrapulmonary symptoms, including renal. In infants and younger children, pulmonary hemorrhage often is not associated with serologic evidence of disease – the true etiology of pulmonary hemorrhage is often not discernible without lung biopsy [9]. Diffuse alveolar hemorrhage may be present in patients following hematopoetic stem cell transplant, associated with diffuse alveolar damage and increased mortality [10, 11].

Over half of infants and children receiving extracorporeal membrane oxygenation (ECMO) have been reported to experience pulmonary hemorrhage [12].These children may have several risk factors for pulmonary bleeding, including necessary anticoagulation, potential infection, and circulatory derangements, as well as the underlying cardiopulmonary pathology precipitating the need for support.

Bronchoscopic Evaluation

The timing and setting of bronchoscopy depend heavily on clinical context. In the otherwise healthy child with low-volume bleeding, the procedure may be done on an elective basis, in an ambulatory fashion. The procedure might be combined with colleagues from gastroenterology, for example, if there is a question of localizing the bleeding to respiratory versus gastrointestinal tract. If, however, the child is critically ill, the procedure is done in a much more urgent fashion, with initial management goals in a large-volume bleed of clearing the airway and establishing effective ventilation.

In the child with a larger-volume bleed who is otherwise stable, bronchoscopy may be performed with anesthesia, usually in the operating room setting. In a patient with CF or coagulopathy, care should be taken to optimize coagulation status, with vitamin K or systemic tranexamic acid [13]. Whether or not to do a computed tomography (CT) angiogram to complement localization efforts is also a consideration. This is especially relevant in a case in which bronchial artery embolization may be appropriate [14]**.** In the critically ill patient in the intensive care setting, bronchoscopy is often done at bedside for localization and diagnostic purposes. Especially in the younger patient on ECMO in whom only a small diameter scope may be passed through the age-appropriate endotracheal tube, there is an option for the placement of a laryngeal mask airway so a larger bronchoscope may be passed, for both diagnostic and therapeutic purposes.

The first step of any bronchoscopy is visual inspection. Care should be taken to evaluate the nasopharynx and upper airway for any potential sources of bleeding. If there is a large-volume bleed emanating from the lungs, even if the source is from a specific location, it may be difficult to pinpoint due to blood in the airway. The airway should be cleared, with care to observe clots. In adults with massive hemoptysis, flexible bronchoscopy localized the source of the bleed in 93% of patients [15]. In general, an arterial source of bleeding will often appear localized, as a greater volume of blood, and may be pulsating. Alveolar bleeds may be high volume in total as well, but the appearance of blood is more diffuse.

Bronchoalveolar lavage (BAL) may provide visually diagnostic information. In an alveolar bleed, successive aliquots may progress from pink-tinged to a more frank bloody appearance. BAL fluid should be sent for routine analyses, including cell count and cultures. Iron staining in macrophages should be assessed [16]. Hemosiderin-laden macrophages should be assessed relative to total count. Of note, breakdown products of hemoglobin are ingested within macrophages within 72 hours [17]. Thus, if this staining is negative, this is likely to be an acute, rather than chronic bleed.

Intervention

Once the bleed has been localized and defined by bronchoscopy, further investigation and intervention can be planned. If the bleed is thought to be secondary to AVM or collateral vessel, CT angiography and/or angiography with coil embolization may be performed. Diffuse bleed in the correct clinical context would prompt additional lab evaluation. Therapeutic strategies such as increasing positive end expiratory pressure (sometimes up to 25–30 cm H_20) and tailoring airway clearance may be initiated. Medical therapies (such as inhaled tranexamic acid [18], steroids, and immunomodulatory drugs) may be started, and the decision to perform a surgical lung biopsy may be facilitated. If bleeding is localized and due to a bronchial artery collateral or pulmonary AVM, bronchial artery embolization may be temporizing or curative [14, 19].

Several interventions may be performed via flexible bronchoscopy. Aliquots of iced saline may be applied to reduce localized bleeding [20], or even temporize massive hemoptysis [21]. Topical application of epinephrine, usually diluted to 1:10,000-20,000, in small quantities, may be performed to similar effect [22]. This must be considered with caution, as side effects include tachycardia and dysrhythmias [3, 23]. Subsequent clots may need to be removed to clear the airway. However, it is important to be aware that these clots may be helping to control the bleeding, and their removal occasionally exacerbates the bleeding with potentially severe hemodynamic consequences.

For massive bleeding confined to a single lung that does not respond to the above strategies, the placement of a double lumen tube to facilitate ventilation of the uninvolved lung may be considered [24]. Bronchoscopic guidance is necessary for correct tube placement and cuff inflation. The same effect may be achieved in a smaller patient by selective intubation of the left lung, or tracheal intubation with balloon catheter occlusion of the left lung. Balloon catheter insertion may also be used to tamponade the bleed when localized, as described in patients with CF and refractory pulmonary hemorrhage [25]. This must be undertaken with caution, to avoid airway and glottis damage. Finally, though not as well-reported in pediatrics, rigid bronchoscopy has a role in controlled removal of an obstructing clot and topical application of anticoagulant while controlling ventilation [22]. The rigid bronchoscope also allows for the deployment of other potential interventions, such as laser cautery and cryotherapy, better described in applications with adults, using larger instruments [20, 26].

Conclusion

Hemoptysis, though uncommon in general, is a relatively common complaint for the pediatric pulmonologist, with a broad differential diagnosis. Flexible bronchoscopy has a clear role in establishing that the lung is the source of the bleeding, localizing the area of bleeding within the lung, establishing the time course of the bleed, and ruling out infection. There are opportunities for therapeutic intervention via both flexible and rigid bronchoscopy that warrant further study.

References

1. Flume PA, Mogayzel PJ Jr, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC, et al. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care Med. 2010;182(3):298–306.
2. Coss-Bu JA, Sachdeva RC, Bricker JT, Harrison GM, Jefferson LS. Hemoptysis: a 10-year retrospective study. Pediatrics. 1997;100(3):E7.
3. Sakr L, Dutau H. Massive hemoptysis: an update on the role of bronchoscopy in diagnosis and management. Respiration. 2010;80(1):38–58.
4. Godfrey S. Pulmonary hemorrhage/hemoptysis in children. Pediatr Pulmonol. 2004;37(6):476–84.
5. Chiel L, Welsh S, Andren K, Mecklosky J, Alexander PMA, Casey A, et al. Pediatric hemoptysis without bronchiectasis or cardiac disease: etiology, recurrence, and mortality. J Pediatr. 2019;214:66–70.
6. Welsh SK, Casey AM, Fishman MP. Pulmonary hemorrhage in infancy: a 10-year single-center experience. Pediatr Pulmonol. 2018;53(11):1559–64.
7. Boat T. Pulmonary hemorrhage and hemoptysis. In: Victor Chernick TFB, Wilmott RW, Bush A, editors.

Kendig's disorders of the respiratory tract in children. Philadelphia: Saunders Elsevier; 2006. p. 66–685.
8. Singla S, Canter DL, Vece TJ, Muscal E, DeGuzman M. Diffuse alveolar hemorrhage as a manifestation of childhood-onset systemic lupus erythematosus. Hosp Pediatr. 2016;6(8):496–500.
9. Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med. 2013;188(3):376–94.
10. Keklik F, Alrawi EB, Cao Q, Bejanyan N, Rashidi A, Lazaryan A, et al. Diffuse alveolar hemorrhage is most often fatal and is affected by graft source, conditioning regimen toxicity, and engraftment kinetics. Haematologica. 2018;103(12):2109–15.
11. Heggen J, West C, Olson E, Olson T, Teague G, Fortenberry J, et al. Diffuse alveolar hemorrhage in pediatric hematopoietic cell transplant patients. Pediatrics. 2002;109(5):965–71.
12. Dalton HJ, Reeder R, Garcia-Filion P, Holubkov R, Berg RA, Zuppa A, et al. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. Am J Respir Crit Care Med. 2017;196(6):762–71.
13. Graff GR. Treatment of recurrent severe hemoptysis in cystic fibrosis with tranexamic acid. Respiration. 2001;68(1):91–4.
14. Monroe EJ, Pierce DB, Ingraham CR, Johnson GE, Shivaram GM, Valji K. An Interventionalist's guide to hemoptysis in cystic fibrosis. Radiographics. 2018;38(2):624–41.
15. Hsiao EI, Kirsch CM, Kagawa FT, Wehner JH, Jensen WA, Baxter RB. Utility of fiberoptic bronchoscopy before bronchial artery embolization for massive hemoptysis. AJR Am J Roentgenol. 2001;177(4):861–7.
16. Faro A, Wood RE, Schechter MS, Leong AB, Wittkugel E, Abode K, et al. Official American Thoracic Society technical standards: flexible airway endoscopy in children. Am J Respir Crit Care Med. 2015;191(9):1066–80.
17. Epstein CE, Elidemir O, Colasurdo GN, Fan LL. Time course of hemosiderin production by alveolar macrophages in a murine model. Chest. 2001;120(6):2013–20.
18. Wand O, Guber E, Guber A, Epstein Shochet G, Israeli-Shani L, Shitrit D. Inhaled tranexamic acid for hemoptysis treatment: a randomized controlled trial. Chest. 2018;154(6):1379–84.
19. Zaidi SJ, Schweig L, Patel D, Javois A, Akhter J. A novel approach to the diagnosis and treatment of hemoptysis in infants: a case series. Pediatr Pulmonol. 2018;53(11):1504–9.
20. Eber E, Antón-Pacheco JL, de Blic J, et al. ERS statement: interventional bronchoscopy in children. Eur Respir J 2017;50:1700901. https://doi.org/10.1183/13993003.00901-2017.
21. Conlan AA, Hurwitz SS. Management of massive haemoptysis with the rigid bronchoscope and cold saline lavage. Thorax. 1980;35(12):901–4.
22. Sidman JD, Wheeler WB, Cabalka AK, Soumekh B, Brown CA, Wright GB. Management of acute pulmonary hemorrhage in children. Laryngoscope. 2001;111(1):33–5.
23. Santhakumar Subramanian AHK, Chhajed PN. Role of bronchoscopy in hemoptysis. In: Jain ACMAP, editor. Interventional bronchoscopy: a clinical guide. New York: Springer Sicence+Business Media; 2013. p. 245–56.
24. Lordan JL, Gascoigne A, Corris PA. The pulmonary physician in critical care * illustrative case 7: assessment and management of massive haemoptysis. Thorax. 2003;58(9):814–9.
25. Jolliet P, Soccal P, Chevrolet JC. Control of massive hemoptysis by endobronchial tamponade with a pulmonary artery balloon catheter. Crit Care Med. 1992;20(12):1730–2.
26. Donato LL, Mai Hong Tran T, Ammouche C, Musani AI. Pediatric interventional bronchoscopy. Clin Chest Med. 2013;34(3):569–82.

29 Flexible Bronchoscopy and Children's Interstitial Lung Disease

Cassandra Aravelo and Maureen Banfe Josephson

ChILD (children's interstitial lung disease) is a term that includes a broad range of pathologies and many rare lung conditions. The estimated prevalence is 3.6 cases per million and the pathogenesis, and natural history remain poorly understood. ChILD can present as a single isolated diagnosis in a patient; however it can also occur in patients with systemic conditions such as rheumatologic disease. ChILD can also present after exposures such as the case of hypersensitivity pneumonitis [1]. ChILD management is complicated by difficulties in making the accurate diagnosis and limitations in evidence-based treatment. Currently, with the exception of genetic testing for surfactant metabolism diseases, open lung biopsy remains the gold standard for diagnosis in chILD [2].

Flexible bronchoscopy represents a potentially useful tool in the evaluation and diagnosis of chILD. A thorough evaluation of airways with flexible bronchoscopy offers some advantages over other diagnostic tools and allows interventional procedures such as biopsy of specific areas, and obtaining samples for cytological and microbiologic analysis [3]. According to the 2013 ATS Clinical Practice Guidelines for the classification, evaluation and management of childhood interstitial lung disease in infancy, the primary benefit of flexible bronchoscopy with BAL in these patients is to obtain specimens for microbiologic analysis in order to rule out infection and to exclude anatomical issues as the cause for the diffuse lung disease.

The direct visualization of the lung parenchyma, evaluation of the anatomy, as well as obtaining biopsies of the bronchioles and bronchoalveolar lavage, fluid may help to assess lung development, mucosal integrity, and disease severity. Direct parenchymal visualization helps to identify mucosal damage as either acute or chronic. In some circumstances, flexible bronchoscopy can even be therapeutic. In cases of pulmonary alveolar proteinosis (PAP), a full lung lavage is both diagnostic and therapeutic.

The analysis of BAL cellular constituents helps to separate inflammatory processes from neutrophil-guided or exogenous damage [4].

When fiberoptic bronchoscopy was introduced to the United States in the early 1970s, there was an immediate impact on the management of certain pulmonary diseases. This diagnostic and therapeutic procedure was first introduced to the pediatric population in 1978, with a delay of approximately 10 years while the development of adequate pediatric bron-

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_29

choscopy equipment and procedures were established [3]. As the procedure became more widespread, direct visualization and exploration of distal airways with the ability to obtain tissue samples and BAL changed the management of pulmonary diseases and particularly some types of chILD. However, as more diagnostic tools are available, the line between investigative use and its legitimate clinical application is more present [5].

This review will evaluate the role of flexible bronchoscopy and BAL analysis in the diagnosis and management of chILD as well as its limitations. Despite a low level of evidence behind this practice, it is a frequently used tool by the pediatric pulmonologist in evaluating a patient with suspected chILD. We will discuss the role of flexible bronchoscopy in evaluating airway anatomy, BAL results, ultrasound evaluation via EBUS, and specific tests and analysis that can be obtained in patients with suspected chILD.

What Is ChILD?

The etiologies of interstitial lung disease in infants and children are clearly distinct from those in older children and adults. Appropriately, steps have been made to better classify the specific diseases that cause both diffuse and interstitial lung disease in children. Despite these classifications, there remains confusion over what constitutes interstitial lung disease (ILD). Fan et al. defined the term "interstitial lung disease" as encompassing a broad spectrum of rare diseases characterized by impaired gas exchange and bilateral diffuse infiltrates on radiographic imaging [6]. The term "ILD" would suggest that these disorders are confined to the interstitium; however, airways and airspace diseases such as bronchiolitis obliterans have also been addressed under the heading of interstitial lung disease, thus leading to even more confusion.

The term "diffuse lung disease" (DLD) is a broad diagnostic category that includes lung disease caused by common primary diagnoses such as cystic fibrosis, congenital or acquired immunodeficiency, congenital heart disease, bronchopulmonary dysplasia, pulmonary infections, primary ciliary dyskinesia, and recurrent aspiration. Once these common diseases that cause DLD have been rule out, a neonate or infant with DLD is regarded as having "chILD syndrome" if they have at least three of the following four criteria: (1) respiratory symptoms (e.g., cough, rapid and/or difficult breathing, or exercise intolerance); (2) respiratory signs (e.g., resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure); (3) hypoxemia; and (4) diffuse abnormalities on chest radiograph or a CT scan [4]. Within the chILD syndrome umbrella, there are specific chILD diagnoses as well as some non-ILD "masqueraders." There are specific chILD diagnoses that occur primarily in the newborn and under 2-year-old age group, and these differ from those encountered in children aged 2–18 years.

Specific chILD diagnoses occurring in the neonatal and under two-year-old age group include: acinar dysplasia, pulmonary hypoplasia/alveolar simplification, alveolar-capillary dysplasia with misalignment of the pulmonary veins (FOXF1 mutations), pulmonary interstitial glycogenosis (PIG), surfactant protein B deficiency (SFTPB mutations), ABCA3 mutations, TTF-1 (NKX2.1) mutations, neuroendocrine cell hyperplasia of infancy (NEHI), alveolar proteinosis (CSF2RA and CSF2RB mutations) pulmonary hemorrhage syndromes, and pulmonary lymphangiectasia [4].

Specific chILD diagnoses occurring in children older than 2 years of age can be separated into three broad categories: idiopathic interstitial pneumonias, primary pulmonary disorders, and ILD associated with systemic disease [6]. The idiopathic interstitial pneumonias include: nonspecific interstitial pneumonia, cryptogenic organizing pneumonia acute interstitial pneumonia, desquamative interstitial pneumonia, and lymphocytic interstitial pneumonia. The primary pulmonary disorders include: alveolar hemorrhage syndromes, aspiration syndromes, hypersensitivity pneumonitis, infectious or post infectious disease (bronchiolitis obliterans), pulmonary alveolar microlithiasis, pulmonary alveolar

proteinosis, pulmonary infiltrates with eosinophilia, pulmonary lymphatic disorders (lymphangiomatosis, lymphangiectasia), and pulmonary vascular disorders (hemangiomatosis). Systemic diseases that can cause ILD in children over 2 include connective tissue diseases, histiocytosis, malignancy-related lung disease, sarcoidosis, and storage diseases.

Diagnostic testing for chILD includes echocardiography to rule out structural cardiovascular disease and pulmonary hypertension, thin-section CT scanning of the chest to characterize the nature and distribution of the lung disease, infant pulmonary function testing, testing for genetic abnormalities associated with diffuse lung disease, flexible bronchoscopy with bronchoalveolar, and surgical lung biopsy.

Table 29.1 Airway conditions associated with chronic pulmonary aspiration identifiable by flexible bronchoscopy

Congenital anatomic abnormalities
Esophageal atresia
Tracheoesophageal fistula
Laryngotrachoesophageal cleft
Choanal stenosis or atresia
Cleft palate
Macroglosia
Larungomalacia
Micrognathia
Vascular ring
Tracheal stenosis
Cystic hygroma
Laryngea/pharyngeal vascular malformation
Acquired anatomic abnormalities
Laryngeal/pharyngeal tumors
Laryngeal/pharyngeal trauma
Tracheostomy

ChILD and Airway Anatomical Evaluation

Flexible bronchoscopy can aid in the evaluation of the airway and pulmonary anatomy. When utilized in the evaluation of a patient with suspected chILD, despite a weak level of evidence for chILD diagnosis [4], an evaluation of the airways is required in order to exclude anatomical anomalies which may be contributing to the symptoms.

Flexible bronchoscopy enables evaluation of the nasopharyngeal, tracheal, and bronchial anatomy and allows for the evaluation of mucosal changes. Anatomical evaluation of the airways includes careful search for malformations such as tracheoesophageal fistula and laryngeal clefts, abnormal bronchial development, and tracheomalacia or bronchomalacia (Table 29.1). In the case of bronchopulmonary dysplasia, a rudimentary anatomy can be observed. Processes such as chronic aspiration, or continuous postnasal dripping, will be evidenced by the changes of the nasopharyngeal and oral mucosa such as inflammatory appearance, increased vascularity, and edema.

In the patient with child, flexible bronchoscopy itself plays an important role in ruling out alternative diagnoses and comorbid conditions that can contribute to the presenting symptoms. However it is important to note that the anatomical evaluation is unlikely to be diagnostic for a specific ChILD diagnosis itself.

ChILD and BAL Results

Bronchoalveolar lavage is the most common method to obtain specimens from the distal airways and alveolar surfaces [15]. It is one of the most important aspects of diagnostic bronchoscopy. During bronchoalveolar lavage, normal saline is instilled into the distal airways via the bronchoscope channel and the fluid returned from the lavage is collected to measure the soluble and cellular contents of the alveolar surface. Since epithelial fluid is not static, it is difficult to estimate the true concentration of substances as it depends on the duration and volume of the fluid employed during lavage. Therefore, specimens obtained by BAL are more useful to evaluate infectious and inflammatory process than for quantitative analysis itself.

BAL should ideally be obtained before starting antimicrobial therapy but can still be informative if the patient is unresponsive to treatment or deteriorating in spite of antimicrobial treatment. Infectious etiologies are detected in the airways of a significant proportion of immunosuppressed infants with DLD or immunocompetent infants

with diffuse pulmonary infiltrates, and occasionally a specific infectious diagnosis can be made this way [4].

In addition to infectious etiologies, BAL analysis is often diagnostic in cases of pulmonary hemorrhage, alveolar proteinosis, and eosinophilic lung disease. In contrast, a normal cell differential often allows the clinician to exclude certain processes such as those noted above. It can aid in the diagnosis of aspiration chronic or acute by the evaluation of the mucosal changes and by obtaining BAL samples for lipid Leyden macrophages [7] or pepsin [8].

The quality of the sample is of paramount importance; therefore, a thorough evaluation of the available pulmonary imaging, along with careful physical examination, is necessary to determine the appropriate anatomical location to pursue for BAL. Flexible bronchoscopy should ideally be timed with other procedures that require general anesthesia in order to reduce the need for multiple anesthetic encounters. Furthermore, if a CT and a lung biopsy are planned, CT imaging should be done first so that an accurate identification of the affected area can be determined. Ideally, the lobe that will be biopsied should be avoided for lavage.

Normal BAL fluid cell count contains less than 5% neutrophils, while neutrophil counts can be as high as up to 95% in cases of bacterial infection [10]. BAL cell count with less than 25% of neutrophils is unlikely to represent a bacterial infection. It is important to keep in mind that an increased neutrophil count can be seen in aspiration, asthma, cystic fibrosis, acute respiratory disease, and alveolitis.

Epithelial cells, and squamous, and ciliated columnar cells are frequently present in normal BAL fluid. The most common non-epithelial cell present in the BAL are alveolar macrophages, which constitute 80–90% of cell counts in the normal lung. Lymphocytes comprise 5–10% of the total normal cell count. While increased level of lymphocytes is a non-specific finding, higher counts are present in some ChILD conditions [11] For example, increased lymphocyte counts can be seen in hypersensitivity pneumonitis, drug-induced pneumonitis, cryptogenic organizing pneumonia (COP), lymphoproliferative disorders as well as in sarcoidosis, *M. tuberculosis* infection, hypersensitivity pneumonitis, *Pneumocystis jiroveci* infection, and non-tuberculous mycobacterial infection (%). Eosinophils are rarely seen in the BAL fluid of healthy children (0–1%) and are seen in a higher predominance in those children with ChILD as well as in those with allergic and parasitic diseases, *Pneumocystis carinii* infection, and drug-induced lung disease [12].

Staphylococcus aureus, *Haemophilus influenza,* and *Streptococcus pneumonia* are common colonizers of the airways. When these organisms are present with a concentration of more than 100,000 organism/mL in association with an elevated neutrophil cell count, this is considered evidence of infection. A bacterial count of more than 500,000 organisms/mL is considered as bacterial infection (%) [11].

Aspiration poses a considerable amount of risk to the lungs. The BAL fluid from lungs affected by aspiration can be prone to culture multiple organisms. Oftentimes, organisms that are not typically considered respiratory pathogens can be cultured from the BAL in immunocompromised children.

Depending on the clinical diagnostic suspicion, additional specific BAL evaluation should be considered. Clear communication between the clinician and laboratory personnel is required in order to ensure adequate handling and processing of the BAL sample. Particular microbiological analysis and culture must be specified including the need for bacterial, viral, and/or fungal culture. Oil Red O staining can be requested for the evaluation of fat-laden macrophages in cases of suspected aspiration. Periodic acid Schiff (PAS) staining is recommended for cases of suspected pulmonary alveolar proteinosis. Iron staining (i.e., Prussian blue) allows for the identification of hemosiderin within macrophages, typical in pulmonary hemorrhage syndromes [9]. Other tests are more specific and less commonly performed, although still beneficial. The presence of CD1a positive cells in the BAL is consistent with the diagnosis of Langerhans cell histiocytosis [13]. A lymphocyte-predominant BAL with a CD4/CD8 ratio may suggest sarcoidosis with the

Table 29.2 Staining of lung biopsy specimens

Stain	Purpose
Always: Haematoxylin and eosin	Overview of extent, distribution, and nature of any pathology
Always: Elastic Van Gieson	Collagen/pulmonary vasculature
As indicated: CD34	Vascular marker
As indicated: Perls stain	Iron laden macrophages
As indicated: Bombesin	Diagnosis of NEHI
As indicated: Periodic Schiff	Glycogen positive cells: PIG
If infection suspected	Ziehl-Neelsen, Grocott, others
As indicated: Immunohistochemistry	Langerhans cells (S-100, CD1a)
Gimesa	Sea-blue histiocyte syndrome [14]

involvement of the lung. Lastly, some metabolic abnormalities may be diagnosed by BAL, for example, sea-blue macrophages with Giemsa staining in the case of sea-blue histiocyte syndrome [14] (Table 29.2).

The utility of serial BAL in the re-assessment and management of pediatric patients with most forms of ChILD remains to be established. Also, endobronchial and transbronchial biopsies are not usually required nor beneficial in making a specific ChILD diagnosis. These samples are too small and the anatomy is severely altered by this technique, which in turn limits interpretation by the pathologist.

Endobronchial Biopsy

The role of endobronchial biopsy (EBB) appears limited to sarcoidosis or cancer staging in adult patient. As for transbronchial biopsy by forceps, the small sample size and related artifact appear to be limiting factors in making an accurate pathologic diagnosis for a specific chILD. Further research and expertise are required to support the use of newer techniques such as EBUS (endobronchial ultrasound) in the diagnosis and workup of chILD in the future. Hopefully there will be methods which might transform and improve our approach to chILD.

CHILD and Timing of Flexible Bronchoscopy

As mentioned above, flexible bronchoscopy is usually done as part of the initial evaluation of a pediatric patient with diffuse lung disease, and whenever it is required, we suggest that it should be timed with other investigations that require general anesthesia. If needed by itself, it should be performed under the same anesthesia as an open lung biopsy.

Repeated Flexible Bronchoscopies in the Management of the Patient with chILD

There is currently no indication of repeated or regularly schedule flexible bronchoscopy in the management of patients with chILD, except in the case of PAP. Patients with PAP often benefit from repeated whole-lung lavage to remove proteinaceous material, which directly impedes oxygenation, from the airspaces. This is typically scheduled on a case-by-case basis, depending on the frequency and severity of the patient's condition.

References

1. American Thoracic S, European Respiratory S. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002;165(2):277–304.
2. Halkos ME, Gal AA, Kerendi F, Miller DL, Miller JI Jr. Role of thoracic surgeons in the diagnosis of idiopathic interstitial lung disease. Ann Thorac Surg. 2005;79(6):2172–9.
3. Soyer T. The role bronchoscopy in the diagnosis of airway disease in children. J Thorac Dis. 2016;8(11):3420–6.
4. Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. Am J Respir Crit Care Med. 2013;188(3):376–94.

5. Perez-Frias J, Moreno Galdo A, Perez Ruiz E, Barrio Gomez De Aguero MI, Escribano Montaner A, Caro Aguilera P, et al. Pediatric bronchoscopy guidelines. Arch Bronconeumol. 2011;47(7):350–60.
6. Fan L, Deterding R, Langston C. Pediatric Interstitial Lung Disease Revisited. Pediatric Pulmonology. 2004;38:369–78.
6. Vece TJ, Fan LL. Interstitial lung disease in children older than 2 years. Pediatr Allergy Immunol Pulmonol. 2010;23(1):33–41.
7. Knauer-Fischer S, Ratjen F. Lipid-laden macrophages in bronchoalveolar lavage fluid as a marker for pulmonary aspiration. Pediatr Pulmonol. 1999;27(6):419–22.
8. Farrell S, McMaster C, Gibson D, Shields MD, McCallion WA. Pepsin in bronchoalveolar lavage fluid: a specific and sensitive method of diagnosing gastro-oesophageal reflux-related pulmonary aspiration. J Pediatr Surg. 2006;41(2):289–93.
9. Bush A, Cunningham S, de Blic J, Barbato A, Clement A, Epaud R, et al. European protocols for the diagnosis and initial treatment of interstitial lung disease in children. Thorax. 2015;70(11):1078–84.
10. Riedler J, Grigg J, Stone C, Tauro G, Robertson CF. Bronchoalveolar lavage cellularity in healthy children. Am J Respir Crit Care Med. 1995;152(1):163–8.
11. Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med. 2012;185(9):1004–14.
12. Oermann CM, Panesar KS, Langston C, Larsen GL, Menendez AA, Schofield DE, et al. Pulmonary infiltrates with eosinophilia syndromes in children. J Pediatr. 2000;136(3):351–8.
13. Refabert L, Rambaud C, Mamou-Mani T, Scheinmann P, de Blic J. Cd1a-positive cells in bronchoalveolar lavage samples from children with Langerhans cell histiocytosis. J Pediatr. 1996;129(6):913–5.
14. Gunay E, Firat Guven S, Aktas Z, Sipit T, Agackiran Y, Erturk H. Pulmonary involvement in sea-blue histiocytosis. Tuberk Toraks. 2012;60(2):176–9.
15. Wood RE, Daines C. Bronchoscopy and bronchoalveolar lavage in pediatric patients. In: Wilmott RW, Bush A, Boat TF, editors. Kending and Chernick's disorders of the respiratory tract in children. 8th ed. Philadelphia: Saunders; 2012. p. 94–109.

Part III

Advanced Diagnostic and Interventional Bronchoscopy

Tracheobronchography

30

Patricio Varela, Michele Torre,
and Nicola Stagnaro

Introduction

TBG is a useful radiologic technique, guided under fluoroscopy, which can provide valuable anatomic and functional information supplementing the endoscopic evaluation in acquired and congenital tracheal bronchial malformations [1].

TBG is a noninvasive procedure, widely available in every radiological unit, and can be performed under general anesthesia in pediatric patients. It is a simple technique, even in those patients under ventilator support or who are anesthetized for other purposes (especially bronchoscopy or cardiac catheterization [2] Figs. 30.1 and 30.2.

TBG is able to delineate the tracheal wall and the bronchial tree of first and secondary order with a high resolution, helping in the visualization of tracheal, bronchial stenosis and complex malformations. This information is particularly helpful for the surgeon, who will be able to have a picture of the whole airway and not only from the endoscopy view [3]. With the use of nonionic iso-osmolar contrast, it is possible to obtain maximum definition of the airway problems, helping for better surgical decisions and surgical treatments (Fig. 30.3a–d).

Early attempts of tracheobronchography used mainly viscous contrast, and many adverse effects were described including coughing, discomfort, bronchospasm, and oxygen hemoglobin desaturation. Diosil contrast, the most extensively used agents in the past, is no longer available. The technique for coating the inside of the walls in the tracheobronchial tree with an opaque contrast material has been in use since the 1920s [4].

There are currently several nonionic, isosmolar contrasts available in the market.

(optiray 320, ultravist 370, visipaque 270, omnipaque)

Precise anatomical definition is important in evaluating and treating patients with tracheal stenosis. Airway endoscopy is the gold standard, but tracheobronchography is complementary when the view is suboptimal or the segment distally to the stenosis is not able to be evaluated by the rigid or flexible bronchoscopes.

TBG can also assess the airway distal to a severe narrowing of the airway, which is often impossible or dangerous to be obtained through endoscopy. In particular in small infants or neonates affected with congenital tracheal stenosis with complete tracheal rings where the

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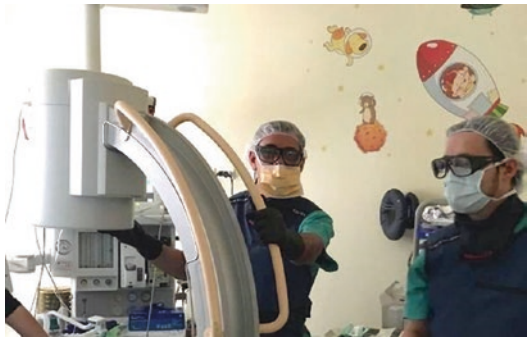

Fig. 30.1 Airway surgeons, with full radioprotection performing a bronchography study in the operation room

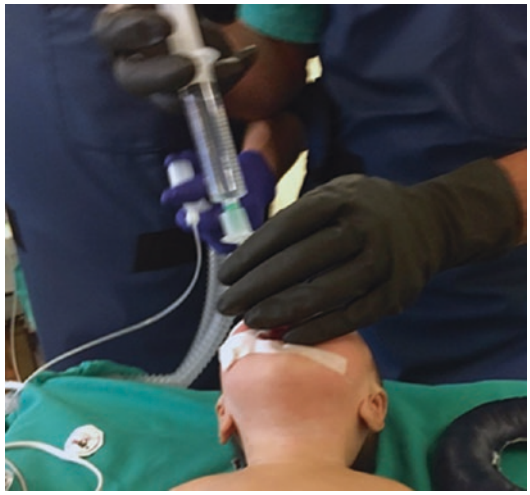

Fig. 30.2 Bronchography study. Patient is in supine position under general anesthesia. The contrast is injected through the tracheal tube using a 4 french nasogastric catheter

airway lumen diameter is sometimes less than 2 mm, making it impossible or dangerous to pass through it with an endoscope. The trauma of an endoscope on a so-small airway and the subsequent edema may have potential catastrophic effects, as ventilation can become impossible and only emergency ECMO can save the life of these patients [5] Fig. 30.4a–c.

TBG may provide essential anatomical information without direct instrumentation of the narrowed portion of the trachea.

A well-performed tracheo-bronchogram by an experienced operator provides information of the main airways without interference with airway dynamics or significant desaturation and is a valuable adjunct to flexible and rigid fiberoptic endoscopy. In some cases, it allows visualizing the segment of airway not reachable with flexible or rigid endoscopes. However, TBG remains an evaluation than complement but cannot substitute airway endoscopy Fig. 30.5a–c.

TBG allows a morphological and dynamic evaluation of the airways, particularly useful to detect the collapse of the tracheal wall during expiration and determine the longitudinal extent of tracheomalacia and the pressure required to maintain airway patency. In this aspect it is similar to dynamic CT scan. The newest application of cine-CT for dynamical evaluation of the airways represents promising non-invasive diagnosing technique, which can potentially modify the diagnostic paradigm of tracheal stenosis [6].

The limited access to CT scan of III generation achievable worldwide by pediatric population and the high dose of radiation required for CT scan are still obstacles to face with. Moreover, in particularly complex patients 3D reconstructions obtained with CT scan are not always as accurate in describing morphology of the airway as TBG [7–9].

Technique

TBG is performed in the operating room or in a digital angiography suite. The patient under anesthesia is on supine position. The oximetry and electrochardiogram are monitorized continuously. We suggest hospitalizing all the patients (Figs. 30.1 and 30.2).

Riebel and Wartner reported that TBG using non-ionic contrast agents is well tolerated by infants and that few patients can experience mild bronchospasm and cough. No changes in the heart rate are observed. It is rare to see pneumonia, edema, or atelectasis.

The newest non-ionic hidrosolubles contrasts are used as mentioned. The total maximum dose recommended is 1–4 ml. The contrast at 50% solution is injected slowly and low pressure into the endotracheal tube using a 4-French nasogastric tube inserted through an airtight connector

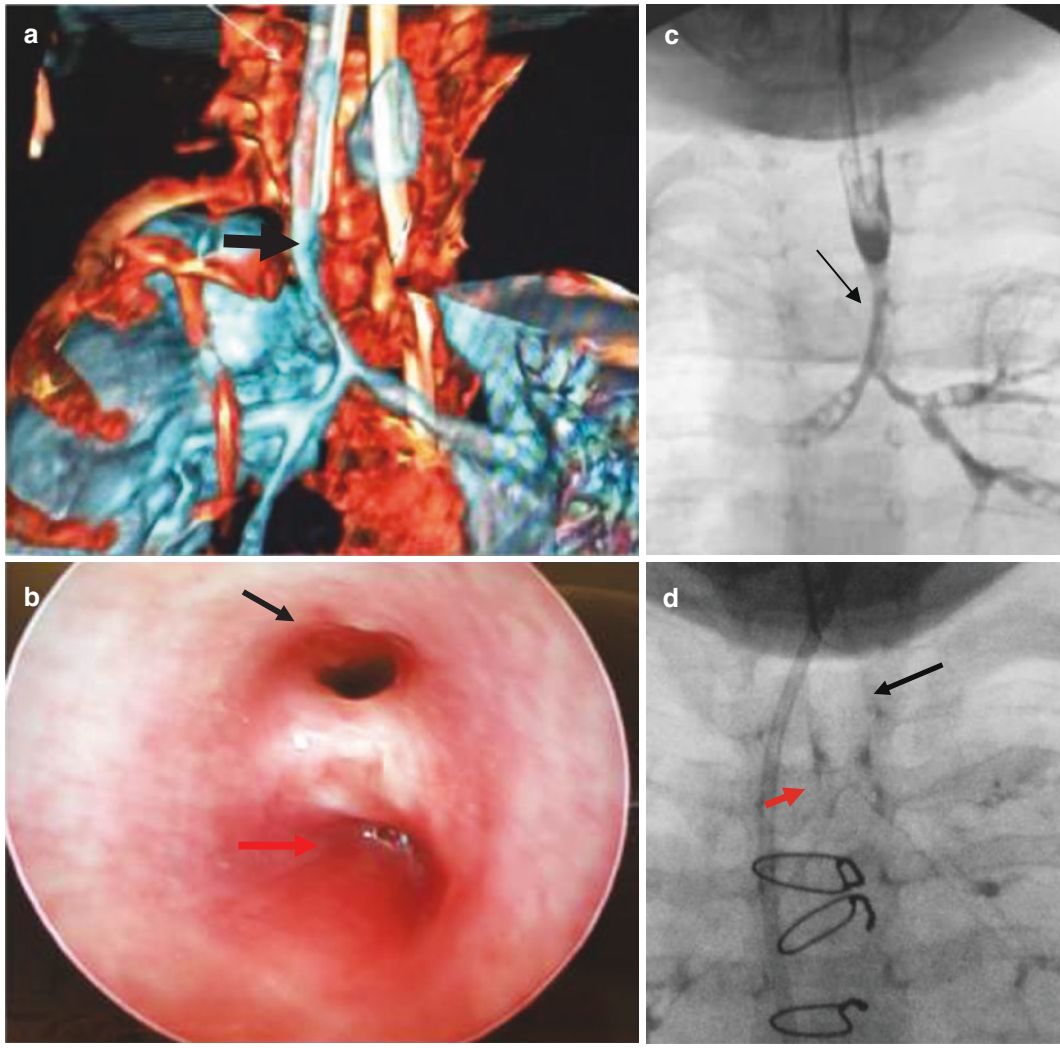

Fig. 30.3 (**a**) Congenital tracheal stenosis. CT scan images. The distal trachea is narrowed with tracheal rings (black arrow). (**b**) Congenital tracheal stenosis endoscopy view shows two lumens. The upper pin hole is the narrowed tracheal lumen (black arrow). Below there is a blind pouch (red arrow). (**c**) Congenital tracheal stenosis. The TBG gives valuable information to the surgeon before the start of the surgery. Distal to the tracheal tube tracheal looks very narrow (black arrow) and bronchus is hiplopasic. Patient underwent a tracheal resection and carinal reconstruction on ECMO. (**d**) Congenital tracheal stenosis. Post-operative bronchoscopy. The stenotic segment was resected. Proximal trachea looks with a normal lumen (black arrow) and carinal reconstruction looks functional (red arrow)

(Fig. 30.2). Contrast can also be injected into the airway down the working channel of a flexible bronchoscope. This is particularly helpful when a laryngeal mask airway is used. Small bronchoscopes have a common working and suction channel, and it may be necessary to pass a 3-French catheter down the working channel to avoid reflux into the suction port [5].

The small amount of contrast produces a thin mucosal coating, which provides a double contrast study with little effect on gas exchange.

The endotracheal tube is withdrawn into the upper trachea, using fluoroscopic guidance. Images of TBF are obtained with different levels of continuous positive airway pressure (CPAP), with the patient breathing spontaneously above

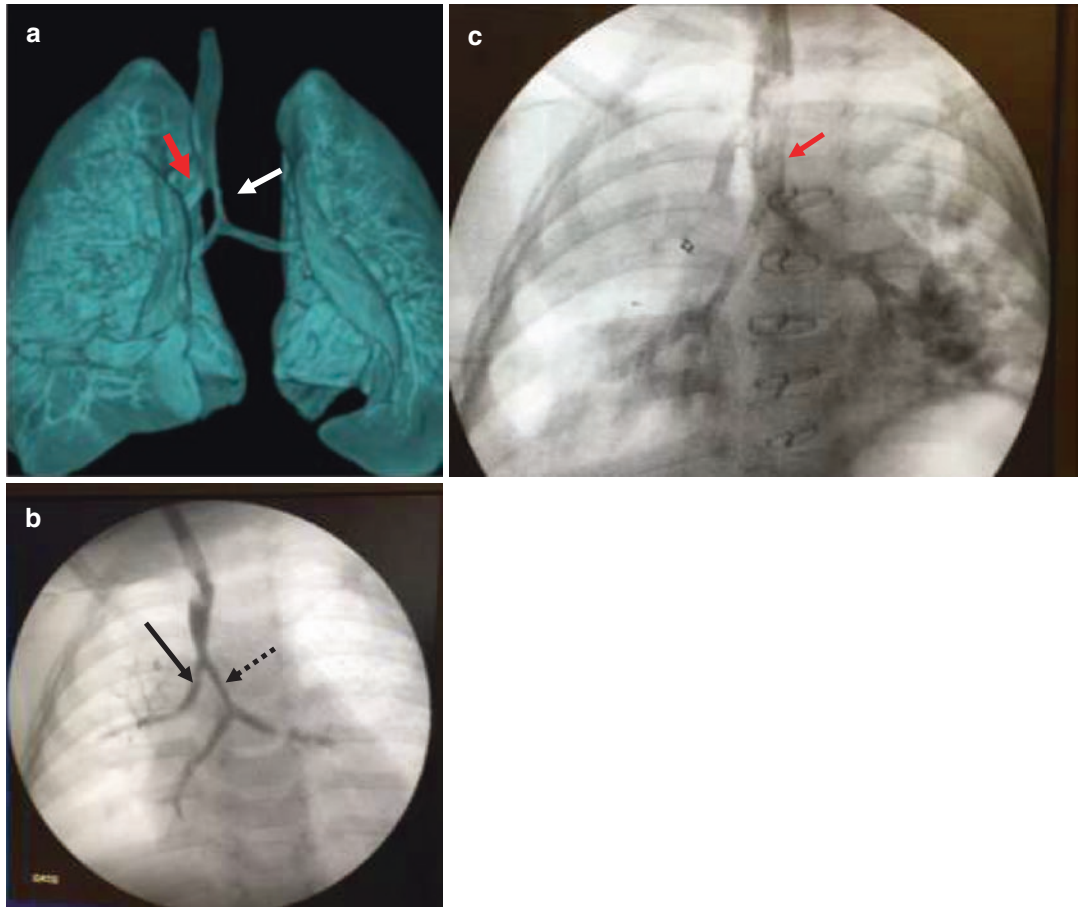

Fig. 30.4 (**a**) CT scan. Congenital tracheal stenosis (white arrow). An upper anomalous bronchus (red arrow). (**b**) Bronchography . Pre-operative bronchography. CTS with the pig or anomalous upper right bronchus (black arrow) arising at the begining of the stenosis (interrupted arrow). (**c**) Post-operative bronchoscopy: after a slide tracheoplasty reconstruction: the tracheal lumen is enlarged (arrow). Compare with the previous preoperative picture

this level of CPAP throughout the study. The response of tracheal caliber to CPAP allows observing the modifications of the airway during dynamic respiratory cycle, which is of paramount importance in those conditions as tracheomalacia in whom diagnosis based on static images can be missed. During bronchography, the anesthesiologist is able to manage the patient's airway disease with precision and confidence [10].

The images are acquired at 6–7.5 frames per second for about 3–5 seconds in anterior-posterior and lateral projections. Because expiratory airway collapse is transient, and the respiratory rate is high, particularly in neonates, a rapid frame rate (5–8 frames per second) is required. It is not appropriate to use higher frame rates, as this does not add diagnostic information and increases the radiation dose for both the patient and the staff. Tracheobronchomalacia can only be adequately assessed when the patient is breathing spontaneously. At the end of procedure, when the procedure is finalized, the contrast medium starts spontaneous absorption, the airway is washed with 2–4 ml of physiologic solution, or the contrast can be suctioned. Adverse events to the procedure are uncommon.

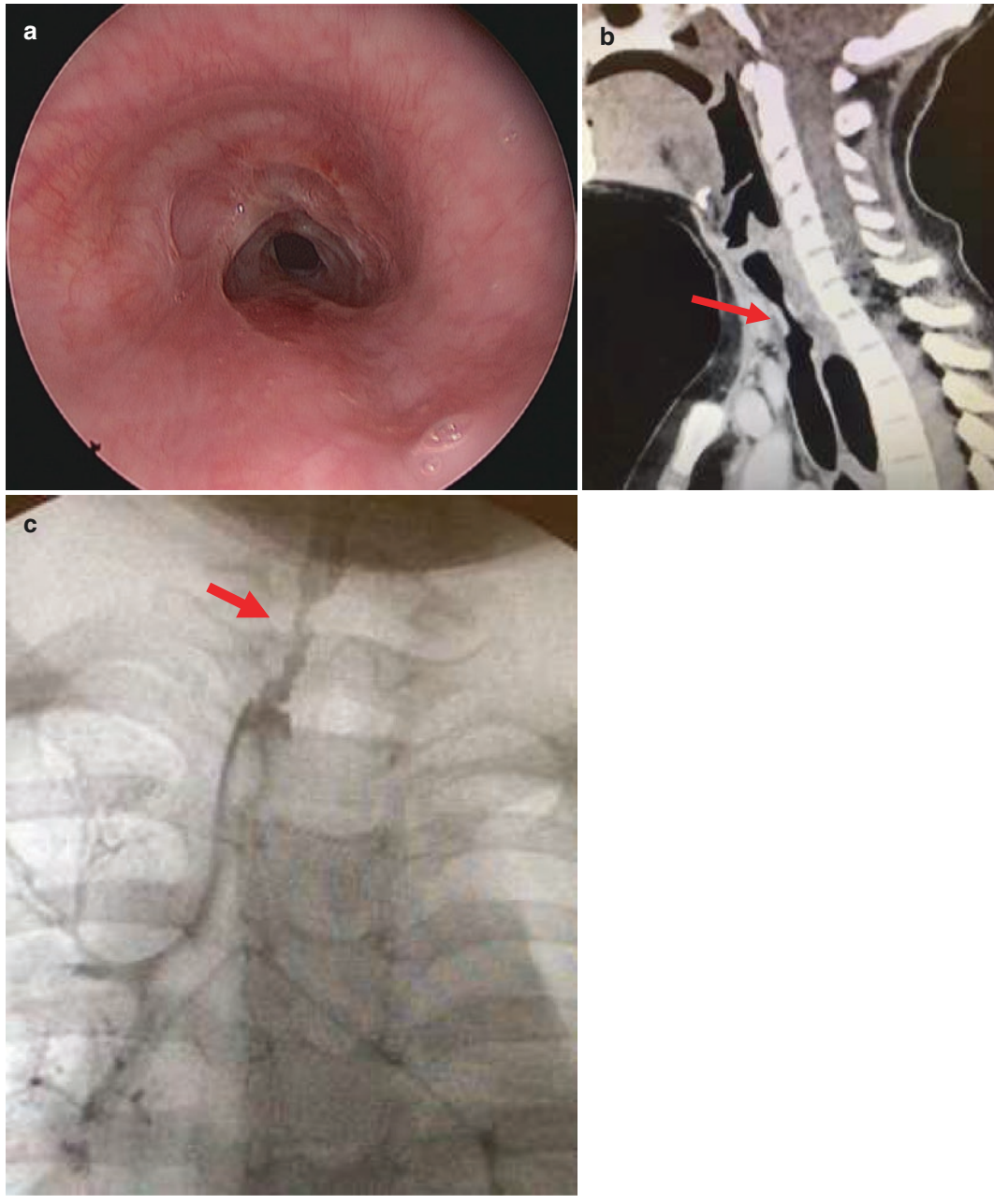

Fig. 30.5 (**a**) Post-intubation tracheal stenosis. Rigid endoscopy view. (**b**) Post-intubation tracheal stenosis CT scan. Tracheal stenosis segment (red arrow). (**c**) Post-intubation tracheal stenosis. Tracheobronchography. Contrast study shows the proxymal stenotic segment (red arrow), irregular mucosal suface, and nornal intrathoracic tracheal and bronchial anatomy

Discussion

In our experience, a very low osmolar contrast medium has been employed with good result without side effects in all the patients. Trachea broncho fluoroscopy (TBF) is necessary to guide the interventional procedures on the airway, as the placement of tracheobronchial bioabsorbable stent [11, 12].

In comparison with endoscopy, TBF had demonstrated a sensitivity of 80% for subglottic, 73% for tracheal, and 80% for bronchial sites of obstruction. It was less sensitive for supraglottic and glottic sites (33% and 14%, respectively). Nasopharyngoscopy is more sensitive for supraglottic and glottic sites of obstruction.

The TBC is also useful in the study of congenital, acquired airway fistulas, and leaking [13] Fig. 30.6a, b.

Brody et al. suggested that TBG may be superior to MRI and flexible bronchoscopy in distinguishing between dynamic and static airway narrowing in selected patients [14].

TBG is indicated for pre-surgical or interventional planning, especially when accurate measurement of tracheobronchial lumen for bioabsorbable stent selection is required [14].

TBG facilitated the interventional procedures in three ways.

First, precise measurement of the airway caliber facilitates the choice of balloon catheters and balloon-expandable stents. Although bronchoscopy examination is useful in identifying the location and nature of airway stenosis, objective and precise measurement of the airway caliber is almost impossible in clinical practice [15].

Second, the "road mapping" of the tracheobronchogram provides accurate landmarks for the inflation of the balloon catheter and the deployment of the stent. Precise positioning of the balloon-expandable bioabsorbable stent is important as adjustment is impossible once the stent is expanded.

Third, tracheobronchography is repeated after the interventional procedures permits immediate assessment of the outcome, with the chance of balloon tracheobronchoplasty when required [16].

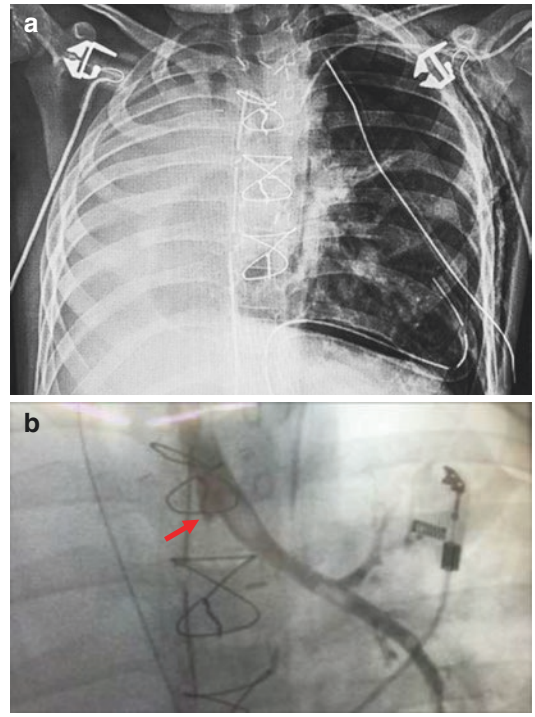

Fig. 30.6 (**a**) X-rays after right neumonectomy in a 7 yo. There is a left neumothorax in the post-operative day 3. Right bronchial leaking is suspected. (**b**) TBG is performed day 3 and shows no leaking through the right bronchial closure (red arrow)

Measurements can be manually performed using the same software used for angiography, with a reference object (15 mm diameter ball). This appears to be much easier and more accurate than trying to make measurements with the bronchoscope [17, 18].

The radiological technique for stent insertion is similar to that for balloon dilatation. In some patients, balloon dilatation will be performed first and a stent inserted only if the airway returns immediately to its previous configuration. Once the area requiring stent insertion has been visualized by bronchoscopy and TBG, measurements of the airway can be taken to ensure the correct size of stent is chosen [5, 17, 18].

Tracheobronchoscopy and Radioprotection

Doses to children from TBF-guided interventional procedures are of special concern because children are more radiosensitive than adults, their life expectancy is longer, and they may undergo repeated procedures [19].

The knowledge of radioprotection fundamentals is mandatory. Fluoroscopy time is the easiest parameter to perceive and control. Minimization of fluoroscopy time has been proven to be one of the most effective ways of reducing radiation dose to the patient and staff during fluoroscopy.

Dose also depends on other factors such as thickness of the imaged body part, field of view, pulse frequency, and dose level of fluoroscopy employed. The radiation exposure of the patient and staff are also dependent on cine images or frame acquisitions.

During TBF, the operator should increase the distance of the X-ray tube from the patient as much as practicable and decrease the distance of imaging detector by as much as practically possible. Most units are equipped with automatic exposure (or brightness) control (ABC) systems.

Keeping a record of the patient dose and avoiding using a large field of view or magnification are effective actions to control and reduce dose [20–24].

References

1. Stagnaro N. et al. Multimodality Imaging of Pediatric Airways Disease: indication and technique. 2017.
2. Dunham ME, Holinger LD, Backer CL, Mavroudis C. Management of severe congenital tracheal stenosis. Ann Otol Rhinol Laryngol. 1994;103:351–6.
3. Corno A, Giamberti A, Giannico S, et al. Airway obstruc- tions associated with congenital heart disease in infancy. J Thorac Cardiovasc Surg. 1990;99(6):1091–8.
4. Deutsch ES, Smergel E, Crisci K, Panitch H. Tracheobronchography in children. Laryngoscope. 1996;106(10):1248–54.
5. McLaren CA, et al. Tracheobronchial intervention in children. Eur J Radiol. 2005;53:22–34.
6. Goo HW. Free-breathing cine CT for the diagnosis of tracheomalacia in young children. Pediatr Radiol. 2013;43:922. https://doi.org/10.1007/s00247-013-2637.
7. Berg E, Naseri I, Sobol SE. The role of airway fluoroscopy in the evaluation of children with stridor. Arch Otolaryngol Head Neck Surg. 2008;134(4):415–8.
8. Rudman DT, Elmaraghy CA, Shiels WE, et al. The role of airway fluoroscopy in the evaluation of stridor in children. Arch Otolaryngol Head Neck Surg. 2003;129(3):305–9.
9. Moq q, et al. Computed tomography versus bronchography in the diagnosis and management of tracheobronchomalacia in ventilator dependent infants. Arch Dis Child Fetal Neonatal Ed. 2005;90:F290–3. https://doi.org/10.1136/adc.2004.062604.
10. Little AF, Phelan EM, Boldt DW, Brown TCK. Paediatric tracheobronchomalacia and its assessment by tracheobronchography. Australas Radiol. 1996;40:398–403.
11. Serio P, Nenna R, Fainardi V, et al. Residual tracheobronchomalacia after surgery for vascular compression in children: treatment with stenting. Eur J Cardiothorac Surg. 2016;15:(pii):ezw299.
12. Antón-Pacheco JL, Luna C, García E, et al. Initial experi- ence with a new biodegradable airway stent in children: is this the stent we were waiting for. Pediatr Pulmonol. 2016;51(6):607–12.
13. Rudman DT, Elmaraghy CA, Shiels WE, Wiet GJ. The role of airway fluoroscopy in the evaluation of stridor in children. Arch Otolaryngol Head Neck Surg. 2003;129(3):305–309.
14. Brody AS, Kuhn JP, Glen Seidel FG, Brodsky LS. Airway evaluation in children with use of ultrafast CT. Pitfalls and recommendations. Radiology. 1991;178:181–4.
15. Doolin EJ, Strande L. Calibration of endoscopic images. Ann Otol Rhino Laryngol. 1995;104:19–23.
16. Cheung YF, Lee SL, Leung MP, Yung TC, Chau AKT, Hui HKY. Tracheobronchography and angiocardiography of paediatric cardiac patients with airway disorders. J Paediatr Child Health. 2002;38:258–64.
17. Antón-Pacheco JL, Comas JV, Luna C, et al. Treatment strategies in the management of severe complications following slide tracheoplasty in children. Eur J Cardiothorac Surg. 2014;46:280–5. 67
18. Vondrys D, Elliott MJ, Mclaren CA, Noctor C, Roebuck DJ. First experience with biodegradable airway stents in children. Ann Thorac Surg. 2011;92:1870–4.
19. Schmid G, Schmitz A, Borchardt D. Effective dose of CT- and fluoroscopy-guided perineural/epidural injections of the lumbar spine: a comparative study. Cardiovasc Intervent Radiol. 2005;29:84–91.
20. Weerakkody RA, Walsh SR, Cousins C, et al. Radiation exposure during endovascular aneurysm repair. Br J Surg. 2008;95:699–702.

21. Geijer H, Larzon T, Popek R, et al. Radiation exposure in stent-grafting of abdominal aortic aneurysm. Br J Radiol. 2005;78:906–12.
22. Storm ES, Miller DL, Hoover LJ, et al. Radiation doses from venous access procedures. Radiology. 2006;238:1044–50.
23. Miller DL, Balter S, Cole PE, et al. Radiation doses in interventional radiology procedures: the RAD-IR study part II: skin dose. J Vasc Interv Radiol. 2003;14(8):977–90.
24. National council on radiation protection and measurements, 2007. Ionizing Radiation Exposure of the Population of the United States, Report 160, Bethesda, MD. 2009.

Functional Endoscopic Evaluation of Swallowing (FEES)

31

Pamela Mudd and Carolyn Noelke

Introduction

Swallowing is a complex problem requiring significant coordination in infants and following a typical maturation process throughout childhood. While the overall parent reported prevalence of dysphagia, or swallowing disorders, in the United States is 0.9%; reports have estimated 25% of normal developing children may have some history of swallowing disorder [1–3]. That number may rise to 80% in children with complex medical problems or developmental delay [3]. Certain populations are at increased risk for dysphagia including premature infants, and infants and children with respiratory difficulty, craniofacial anomalies, cardiac conditions and history of cardiac surgery, neurologic dysfunction, central nervous system injury or malignancy. Various syndromes including CHARGE, Down (Trisomy 21), and DiGeorge (22q11.2) are associated with dysphagia [4–6]. This list of course is not all-inclusive.

Diagnosis of dysphagia requires review of underlying diagnosis, respiratory status, oral motor function, and importantly airway safety during swallow. Various ways to evaluate swallow are available and include clinical feeding evaluations, videofluoroscopic swallowing studies (VFSS) including modified barium swallow study (MBSS) in conjunction with speech language pathology (SLP), and, of importance to this textbook, functional endoscopic evaluation of swallow (FEES) with or without evaluation for sensory testing (FEESST).

Langmore and colleagues described the FEES exam in 1988 as a procedure to assess oropharyngeal dysphagia [7]. Pediatric application of FEES was developed in 1995 by Willging and further described in 2000 [8, 9]. In FEES, a flexible fiberoptic or distal chip endoscope is introduced trans-nasally to view laryngeal, pharyngeal, and hypopharyngeal structures from above at the level of the palate. Initially, the patient's anatomical structures are assessed at baseline. The patient is then led through various tasks to evaluate the motor and sensory status of the pharyngeal and laryngeal swallow. This chapter will discuss the instrumentation, the technique, and the evaluation, as well as explore some of the more important literature showing evidence to support FEES as a diagnostic examination in pediatric dysphagia.

Patient Selection

Indication for FEES may include the desire to assess the ability to protect the airway during swallowing. FEES may be specifically selected for the evaluation of swallow in a patient with

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*,
Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_31

known or suspected structural abnormalities of the pharynx or larynx, difficulty managing secretions, evaluation before and after airway surgery, and as a follow-up examination in children requiring serial exams to track progress. FEES has advantages, including avoidance of radiation (as required in VFSS/MBSS), ability to test children in natural feeding positions including during breastfeeding or while in a wheelchair, ability to visualize the larynx directly for signs of anatomical or neurologic differences that may impact feeding, and the ability to test even small volumes of liquid or even saliva.

Though the exam is technically an invasive evaluation, it is typically well tolerated and can offer valuable information [8]. Recent publications have credited its value in neonatal intensive care units, have favored the results over those of VFSS, and have suggested the value of FEES as a compliment to VFSS as well as in continuity in evaluation [9–11]. The examination is safe with relatively low risk. Adverse reactions are primarily related to the invasive nature of the exam and may include discomfort, inability to calm for oral intake, nose bleeds (epistaxis), gagging/vomiting, and rarely laryngospasm.

Instrumentation

FEES is an evaluation in swallowing completed with a flexible endoscope attached to a video recording system to allow simultaneous capture of real time images, as well as for review and at times slow motion playback. Flexible endoscopes are available in multiple sizes with the most commonly used scope size for pediatric patients between 2 and 4 mm. The technology of the scope may be a fiberoptic endoscope or a distal tip-in-chip scope with standard or high-definition imaging capability. The scope used should be the smallest scope that allows for the most optimal image quality available. Portable systems are available that can be adapted for mobile use, especially useful for inpatient examinations.

Technique

FEES evaluation can be completed in an inpatient or outpatient setting in a team evaluation with SLP and otolaryngology. The SLP role includes reviewing swallow and medical history, evaluation of the patient's voice/speech, completion of a bedside evaluation prior to instrumentation, judges swallow dynamics, feeds the patient during the exam, and provides recommendations and compensatory strategies in real time to aid with dysphagia [12]. The role of the otolaryngologist (ENT) is to review the medical and surgical history, pass the scope and maintain visualization, evaluate the anatomical structures and neurologic function, and assess secretion management and sensation as appropriate. A collaborative approach is taken to determine management decisions.

The ENT may use topical anesthesia as well as a decongestant to perform the exam. Techniques for the use of these medications vary. Studies assessing the safety of use of FEES have shown that the use of a decongestant, such as oxymetazoline, can improve the ability to pass the scope through the nasal cavity and nasopharynx. Topical anesthetic can be applied directly to the nasal cavity or to the scope itself while it is passed. The anesthetic can lead to decreased sensation, which could affect swallowing. However, studies examining the use of anesthetic on the scope during introduction have not shown increased dysphagia [13]. Contraindications to use of topical treatment include age <1 year of age, neurologic deficit, and known allergy to spray components.

The scope is used to evaluate both the right and left nasal passage, evaluating the nose for congestion or anatomical differences, is then passed into the nasopharynx where palatal closure and adenoid obstruction can be evaluated, then curved over the soft palate along the posterior pharyngeal wall for an overview of the pharyngeal walls, base of tongue and vallecula, position of the epiglottis in relation to the vocal folds and airway, exam of the vocal folds and immediate subglottis through a translaryngeal view, evalua-

tion of neurologic tone and mobility of the laryngeal structures and vocal folds, evaluation of the posterior cricoid and hypopharynx, and appreciation of secretions at baseline. Sensation can be tested through specialized scope that allows for a puff of air to be released over the larynx to assess for reflexive closure in response to the pressure created. A simple touch of the scope to the side of the larynx can also assess this reflex.

Various techniques can then be used by the SLP to evaluate the laryngeal and pharyngeal structures before and after a swallow as discussed in evaluation. It is important to understand that FEES does not assess the actual moment of a swallow, as a "white out" period will appear on the screen during a swallow, if not impaired. The entire examination is recorded in real time for review. Once all tasks are complete, or once the patient is no longer willing or able to complete a useful examination, the scope is removed from the patient slowly reversing out of the pharynx, into the nasopharynx, and through the nasal cavity.

Evaluation

Prior to completing a FEES evaluation, there are multiple considerations for candidacy and the need to undergo FEES. It is recommended that a speech-language pathologist complete a clinical bedside feeding evaluation to assess normal eating at the bedside without interventions and determine if other interventions can be implemented prior to the need for an instrumental assessment. If during the clinical bedside evaluation, the clinician has concerns for aspiration and interventions do not seem to improve signs and symptoms for aspiration, it is then recommended that an instrumental assessment be completed to assess anatomical structures. Additionally, an otolaryngologist may complete a bedside examination of anatomical structures initially and determine to consult a speech-language pathologist.

FEES examination may be chosen as the optimal evaluation over VFSS in certain situations, may be used as an adjunct to VFSS, and is also optimal for follow-up examinations to determine patient progress. It is important to note the concerns of dysphagia and rationale for evaluation in determining the most appropriate standardized assessment. For instance, if a patient presents with increased congestion, coughing, watering eyes, and desaturations with feeds, then a VFSS/MBSS in conjunction with radiology should be performed as endoscopic instrumentation may worsen the congestion and may miss silent aspiration. If a patient is demonstrating difficulty managing their own secretions, shows minimal interest in oral feedings, or exclusively breastfeds the volume need for VFSS/MBSS may be restrictive. In addition, if there are concerns for anatomic abnormality in the setting of dysphagia, a FEES may be considered as anatomic evaluation can be completed in conjuction with the swallow exam. Additionally, it is important to note that many factors come into play with determining appropriate assessment tools, including safety of transfer to a radiology suite.

It is important for the evaluation that the patient is able to be calm during the examination to obtain the best results. Factors to consider to aid in a successful exam include decreasing the number of people present in the room, having parents close by, offering a pacifier for the patient to calm, using bottles, cups, or utensils the patient is comfortable with, and using a smaller endoscope. The FEES protocol assesses Pre-swallowing Tasks in Part I and the Ability to Swallow Food and Liquid in Part II [7]. Part I includes the assessment of the anatomy, baseline secretions, key structural movements, and sensory physiology related to swallowing. Swallowing dynamics including swallow response time, degree of and response to penetration and/or aspiration, and degree and clearance of residue may be assessed during this stage. Part II is primarily at the discretion for the examiner as it directly relates to a patient's specific needs or concerns. The patient's overall laryngeal anatomy is assessed prior to introducing various food consistencies, as above. It is important that a speech-language patholo-

gist is present to provide study interpretation and interventions, and introduce compensatory strategies if applicable.

Compensatory strategies can be introduced after initial evaluation. The type of compensatory strategies differs depending on age and neurologic status. Infant strategies may include changes in positioning, pacing, flow rate/nipple, +/− thickeners. In children and adolescents strategies such as verbal cueing, mechanism of delivery changes such as the use of straw versus cup, alternating solids and liquids to assist with clearance, chin tuck or other positioning strategies, hard or dry swallows, and altering consistency +/− thickeners may be used. The overall clinical evaluation, in addition to the standardized assessment completed during the FEES exam, enables the SLP and otolaryngologist to provide appropriate recommendations for a feeding plan of care individualized for each patient.

Scoring Systems

The scoring system for FEES has not yet been standardized or validated in the adult or pediatric population. Two particular parameters scored on a FEES examination have received the most attention for research publications: penetration/aspiration and bolus clearance or residue [6]. The Penetration-Aspiration Scale (PAS) [11], which assesses depth, location, and response to penetration and aspiration, is used at some facilities; however, there is no specific standardization. Residue scoring systems have been developed as well but have not been standardized, and not validated in pediatric FEES. In addition it is noted that such scores alone are not able to determine a diagnosis or to be used as a guide for treatment, though with improved validity a FEES guideline may allow for more consistent evaluation.

Evidence

The first pediatric FEES studies published assessed acceptance of the technique in children, compared FEES and VFSS, and found agreement in the diagnosis of penetration and aspiration [7, 8]. FEES was noted as superior for the evaluation and diagnosis of anatomic abnormalities, residue, and premature spillage [8]. In 2000 a blinded comparative study between FEES and VFSS additionally discussed the feasibility of FEES as a technique for both diagnosis and treatment of pediatric dysphagia [12]. Although not a pediatric publication, much can be learned from the review published on FEES, which describes the techniques and evaluation, and discusses literature on anesthetic effects on swallow and endoscope tolerance as well [13].

The neonatal, and especially the premature population is specifically susceptible to dysphagia. In 2016 Reynolds et al, published a review of pediatric FESS and developed a multidisciplinary FEES program in the neonatal intensive care unit (NICU) [9]. The efficacy and validity of FEES versus VFSS in the evaluation of infants <3 months of age was then completed. This study showed no adverse events, validating the safety of the examinations in young infants. In addition the FEES was reliable in detecting penetration and aspiration in bottle fed infants under 3 months of age with an inter-rater reliability of 80% compared to 87–90% with VFSS [10].

FEES is the only instrumental feeding evaluation that can be used to assess dysphagia in a breastfeeding infant. In 2016 a case series on 23 infants <10 months of age showed FEES during breastfeeding was safe and effective. Greater than 90% of the infants were able to complete the exam and participated in active breast-feeding during the evaluation. Compensatory strategies were offered after the completion of the exam [14].

References

1. Bhattacharyya N. The prevalence of pediatric voice and swallowing problems in the United States. Laryngoscope. 2015;125(3):746–50. https://doi.org/10.1002/lary.24931. Epub 2014 Sep 15
2. Arvedson JC. Assessment of pediatric dysphagia and feeding disorders: clinical and instrumental approaches. Dev Disabil Res Rev. 2008;14:118–27.

3. Svystun O, Johannsen W, Persad R, Turner JM, Majaesic C, El-Hakim H. Dysphagia in healthy children: characteristics and management of a consecutive cohort at a tertiary centre. Int J Pediatr Otorhinolaryngol. 2017;99:54–9. https://doi.org/10.1016/j.ijporl.2017.05.024. Epub 2017 May 30
4. White DR, Giambra BK, Hopkin RJ, Daines CL, Rutter MJ. Aspiration in children with CHARGE syndrome. Int J Pediatr Otorhinolaryngol. 2005;69(9):1205–9.
5. Jackson A, Maybee J, Moran MK, Wolter-Warmerdam K, Hickey F. Clinical characteristics of dysphagia in children with down syndrome. Dysphagia. 2016;31(5):663–71. https://doi.org/10.1007/s00455-016-9725-7. Epub 2016 Jul 12
6. Eicher PS, McDonald-Mcginn DM, Fox CA, Driscoll DA, Emanuel BS, Zackai EH. Dysphagia in children with a 22q11.2 deletion: unusual pattern found on modified barium swallow. J Pediatr. 2000;137(2):158–64.
7. Langmore SE. History of fiberoptic endoscopic evaluation of swallowing for evaluation and management of pharyngeal dysphagia: changes over the years. Dysphagia. 2017;32(1):27–38. https://doi.org/10.1007/s00455-016-9775-x. Epub 2017 Jan 18. Review.
8. Willging JP. Endoscopic evaluation of swallowing in children. Int J Pediatr Otorhinolaryngol. 1995;32(Suppl):S107–8.
9. Hartnick CJ, Hartley BE, Miller C, Willging JP. Pediatric fiberoptic endoscopic evaluation of swallowing. Ann Otol Rhinol Laryngol. 2000;109(11):996–9.
10. Reynolds J, Carroll S, Sturdivant C. Fiberoptic endoscopic evaluation of swallowing: a multidisciplinary alternative for assessment of infants with dysphagia in the neonatal intensive care unit. Adv Neonatal Care. 2016;16(1):37–43. https://doi.org/10.1097/ANC.0000000000000245. Review
11. Suterwala MS, Reynolds J, Carroll S, Sturdivant C, Armstrong ES. Using fiberoptic endoscopic evaluation of swallowing to detect laryngeal penetration and aspiration in infants in the neonatal intensive care unit. J Perinatol. 2017;37(4):404–8. https://doi.org/10.1038/jp.2016.239. Epub 2017 Jan 5
12. Role of the Speech-Language Pathologist in the Performance and Interpretation of Endoscopic Evaluation of Swallowing: Guidelines. 2004. https://doi.org/10.1044/policy.gl2004-00059
13. Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. Dysphagia. 1996;11(2):93–8.
14. Leder SB, Karas DE. Fiberoptic endoscopic evaluation of swallowing in the pediatric population. Laryngoscope. 2000;110(7):1132–6.

Bronchoscopy in Pediatric and Neonatal ICU

32

Jonathan Puchalski

There are various indications for admission to the neonatal or pediatric intensive care unit and, therefore, a myriad of underlying disorders resulting in respiratory failure. Both diagnostic and therapeutic bronchoscopy have important roles in the ICU; however, the practitioner must understand the technical aspects, inherent risks, and limitations of the procedure in order to appropriately determine the need for bronchoscopy in critically ill children.

According to a 2015 ATS official document regarding technical standards for flexible airway endoscopy (FAE) in children, the primary reason for performing endoscopy is when, "based on the available clinical data, the need for intervention from or intervention within the lungs or airways is most safely, effectively and easily achieved by FAE" [1]. The general indications include anatomical evaluation of the upper and lower airways and bronchoalveolar lavage (BAL) to evaluate persistent or recurrent infiltrates, community-acquired or ventilator-associated pneumonia, pulmonary infections in immunocompromised hosts, and pulmonary hemorrhage (Table 32.1). Notably, the optimal manner of performing BAL has not been systematically investigated and the interpretation of various markers found in BAL fluid remains uncertain. The committee offering the ATS standards recognized the only absolute contraindication to bronchoscopy is refusal by the parent or guardian of the child. Pre-procedural optimization may allow safe completion of bronchoscopy in the setting of coagulopathy, pulmonary hypertension, cardiovascular instability, and severe hypoxemia and respiratory failure.

Table 32.1 Indications for flexible bronchoscopy in the ICU

Diagnostic bronchoscopy	Therapeutic bronchoscopy
Unexplained stridor or wheeze	Bronchoscopic intubation
Suspected structural abnormality	Treatment of atelectasis
Suspected endobronchial lesion	Evaluation and control of hemorrhage
Recurrent pneumonia	Dilation of stenosis
Microbiologic sampling (immunocompromised)	Other interventions, when appropriate (laser/ablation, stenting, whole lung lavage, other)
Suspect aspiration	
Abnormal radiographic finding	

Adapted from Refs. [1, 5]

For bronchoscopy in critically ill children, the procedure is often limited to inspection and BAL. If performed to guide intubation, a bougie or airway exchange catheter may be required. "Specialized" procedures and supplies may include transbronchial aspiration needles, biopsy forceps (1.0 and 1.8 mm), grasping for-

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_32

ceps, retrieval baskets, cytology brushes (1.0 and 1.8 mm), snares, and fluoroscopy [1]. Notably, many if not most tools used in pediatric bronchoscopy require a 2.0 mm suction port for passage.

The airway is typically approached transnasally, transorally, through an endotracheal tube (ETT), or through a tracheostomy. In non-intubated patients, a face mask or laryngeal mask airways (LMA) may provide support. Bronchoscopy through an ETT does not examine the upper airway (oropharynx, larynx, vocal cords, and upper trachea) and may cause airflow resistance and complications, described in detail later. Similarly, the LMA bypasses the nostril to the glottis and distorts laryngeal anatomy and dynamics [1]. Notably, the stated diameter of the bronchoscope may actually be larger than advertised [2]. These limitations may be important in diagnostic bronchoscopy.

Many if not most of the patients encountered in the NICU or PICU will be intubated, indicating both extreme physiologic distress and a higher potential for complications with interventions. An adaptor with a slit diaphragm provides a better seal around the bronchoscope than those with a fixed opening [3]. The size of the endotracheal tube is vitally important as the bronchoscope obstructs a significant portion of the ETT, thus limiting air flow and possibly contributing to hypoxia, increased pulmonary vascular resistance, and inadvertent positive end expiratory pressures (PEEP). The smaller bronchoscopes have limited suction capability, limiting their potential uses in the ICU to visualization and perhaps bronchoalveolar lavage. In these scenarios, therapeutic bronchoscopy may be difficult, albeit not impossible. Endotracheal and bronchoscopic sizes to consider are shown (Table 32.2). Notably, it is recommended that the ETT be at least 1 mm larger than the outer diameter of the bronchoscope to minimize airflow resistance. In select circumstances, such as those when guiding intubation, a lubricated bronchoscope can sometimes fit into a relatively smaller ETT. The formula to determine the proportion of the cross-sectional area that the ETT blocks is: [1-(bronchoscope radius^2/ETT radius^2) x 100]. Using this, the estimated percentage of obstruction ranges from 8–72% with an accompanying increased airway resistance greater than 70 times baseline [3, 4]. Expertise is required to ensure safety in these scenarios.

Table 32.2 Chart estimating age of child, size of endotracheal tube often used if intubated, and size of bronchoscope/suction channel for Olympus-manufactured scopes

Age of child*	ETT size**	Scope diameter (mm)	Suction channel
Preterm	3.0	2.2 mm	None
<24 months	3.5–4.0	2.8 mm	1.2 mm
2–4 years	4.5–5.5	2.8–3.8 mm	1.2 mm
4–8 years	5.0–6.5	4.0 mm	2.0 mm
8–18 years	>6.5	4.9 mm and above	Up to 3.2 mm

Pentax and other manufacturers have similar sizes available for flexible bronchoscopes. The associated ETT size and age of the child (*, **) are estimated

Technical Aspects and Physiologic Considerations

Safety is an essential consideration when performing bronchoscopy in the intensive care unit as the patients are more tenuous than outpatients and often there are systemic considerations beyond oxygenation and ventilation. Preexisting conditions requiring special consideration include upper or central airway obstruction, severe bronchial hyperresponsiveness, hemodynamic instability, severe or uncontrolled pulmonary hypertension, uncorrected bleeding diatheses, immunodeficiency, and infectious risks to the operators [5].

Essentials include IV access; pulse oximetry; occasional capnography; and monitoring of blood pressure, heart rate, respiratory rate, and other parameters. Assistance is essential with one provider managing sedation or anesthesia, typically an intensivist or anesthesiologist, and appropriate adjunct personnel in the room such as nurses, respiratory technicians, and others. The bronchoscopist should be able to focus on the procedure at hand and communication with others.

As noted above, the smallest flexible bronchoscopes have limited suction capability. Furthermore, the fiber optics are adequate but

often provide less clarity than larger video and high-definition bronchoscopes. When BAL is performed, non-bacteriostatic normal saline is typically instilled, although neither the optimal volume nor the number of aliquots has been established. Similarly, the minimum amount of BAL fluid necessary to perform the requested studies varies by institution. Additional logistics regarding BAL specimen collection are beyond the scope of this chapter.

Rigid bronchoscopy is sometimes required for ICU patients but may be very difficult to perform at the bedside. In the ICU setting, its use includes removal of foreign bodies, control of brisk hemorrhage, and for interventional techniques such as stent placement or debulking of endobronchial lesions. In general, the glass rod telescope offers superior views of the posterior larynx and subglottic space [1]. Rigid bronchoscopy is covered in more detail elsewhere.

Physiology

An increase in airway resistance occurs during bronchoscopy through an ETT. When receiving mechanical ventilation, there is also an increase in peak inspiratory pressure (PIP) and positive end expiratory pressure (PEEP) with a decrease in tidal volume delivered related to the obstruction caused by the bronchoscope and the impact of suctioning. Oftentimes the ventilator may need to be adjusted to accommodate for these changes, including increasing the FiO2 to 1.0 throughout, increasing respiratory rate and decreasing PEEP. Sedatives, anxiolytics, narcotics, and muscle relaxants may be considered during the procedure, as dictated by individual circumstances.

In volume control mode, PIP tends to be impacted most, whereas in pressure control ventilation tidal volume is decreased. Significant changes in PIP and tidal volume were demonstrated during bronchoscopy in a pediatric lung model, including changes in tidal volume by 50% and increases in PIP by ≥20 cm H_20 [6]. Suctioning may further contribute to alveolar collapse, atelectasis, and decrease lung compliance while saline instillation is felt to wash out surfactant [3].

Hypoxia is one of the most common problems during bronchoscopy in the ICU. This may be due to decreased tidal volume and atelectasis, suctioning, and localized alveolar flooding from saline instillation. Hypercapnea may occur due to hypoventilation. Although typically well tolerated, it may cause worsened pulmonary hypertension due to vasoconstriction and worsen cerebral edema due to vasodilation [3].

Cardiovascular effects include pulmonary arterial vasoconstriction, increased intrathoracic pressure affecting venous return or left ventricular output, and tachycardia or hypertension related to anxiety or discomfort. An increase in PEEP may have a significant impact on cardiac output, especially in patients dependent on adequate systemic blood pressure and low pulmonary vascular resistance, such as those who underwent Glenn or Fontan procedures for the correction of congenital heart defects. Additionally, high PEEP may increase central venous pressure and consequently increase intracranial pressure [3].

Systemic Review of Flexible Bronchoscopy in Critically Ill Pediatric Patients

A systemic review performed in 2015 addressed the outcomes of flexible bronchoscopy in critically ill children [5]. This review included 27 studies, two-thirds of which were retrospective. Most procedures were performed at the bedside with the notable exception being evaluation for esophageal atresia. In 4/27 (15%) of the studies, patients were on extracorporeal life support (ECLS). The authors found that bronchoscopy was integral in changing patient's care in 1/3 of patients. This included patients without known respiratory anomalies requiring surgical planning, such as those with esophageal atresia or congenital heart disease. It was also important for altering medical management beyond antibiotics, such as endotracheal suction techniques for those with airway granulomas.

Diagnostic Bronchoscopy

The diagnostic yield of bronchoscopy varied with different patient populations, as expected. The highest yield was in patients with extubation failure (69.9% diagnostic yield), congenital heart disease (57.5%), those with hemoptysis (56%), and those requiring ECLS (31%). In each of these scenarios, anatomic problems were prominent, such as mucus plugging, airway compression, malacia, and malpositioned or occluded endotracheal tubes.

One of the most common indications for flexible bronchoscopy in the NICU is abnormal breathing sounds such as stridor or wheezing. These may be due to congenital abnormalities of the upper or lower airways, associated with problems from prior intubation (subglottic stenosis or vocal cord injury), or due to other issues such as recurrent laryngeal nerve injury. Additionally, the bronchoscope may be used to guide intubation or to ensure appropriate placement of the endotracheal tube. For example, tracheomalacia may mandate ETT placement close to the carina, bleeding may require single lung ventilation, and congenital anatomic abnormalities may prevent normal jaw opening during direct laryngoscopy [3].

Most studies used BAL for the investigation of infectious etiologies causing respiratory failure or radiographic abnormalities. Although infections can often be identified from tracheal suctioning along with adjunctive nasal washings (Viral PCR), BAL may help distinguish true infections from colonization and may identify organisms difficult to identify otherwise, such as Pneumocystis jirovesii, mycobacterial, fungal, and opportunistic infections [3]. In 12 studies indicating BAL as a common indication for the procedure, an infectious organism was found in 25.7%. The highest yield for a specific organism was in immunocompromised patients (79.1%) whereas an organism was found in 30.3% of patients requiring ECLS. Therapy was changed in 50% of patients as a result of the BAL findings in one study [7]. The concordance between blind tracheal swab isolates and BAL isolates was 47% [7, 8]. In addition to immunocompromised patients, BAL was particularly useful in patients with an abnormal chest X-ray not responding to antibiotics.

Therapeutic Bronchoscopy

The therapeutic yield of flexible bronchoscopy in the ICU was 60.3%. Therapeutic interventions included lavage, removal of partial obstructions, and assistance with difficult intubation or failed extubation. Atelectasis improved in 44.9% of procedures. In neonatal patients, this number reached 75% [8]. Bronchoscopy assisted in successful extubation in 69.9% of procedures by removing mucus plugs or thrombus and by identifying those patients with normal exams [5]. Fig. 32.1 demonstrates endoscopic findings of mucus plugging and a large thrombus "cast" of the airways.

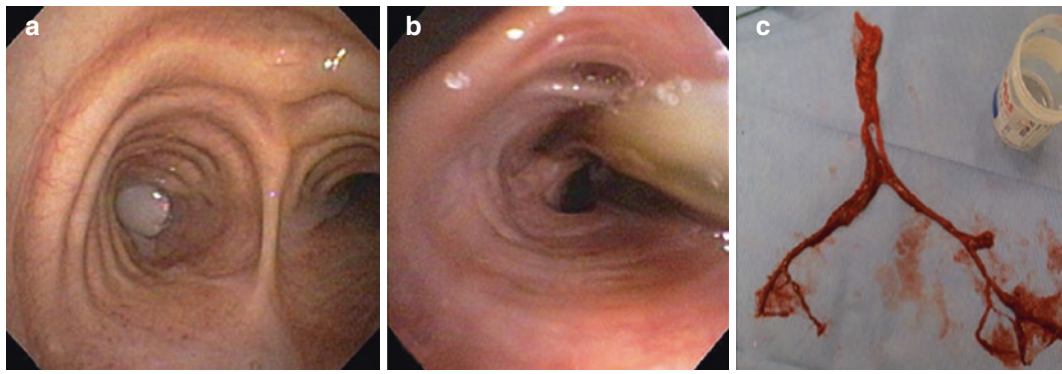

Fig. 32.1 (**a**) Mucus plug in left mainstem bronchus. (**b**) Mucus plug being aspirated into bronchoscope. (**c**) Airway "cast" caused by hemoptysis

In specialized populations, therapeutic bronchoscopy was also found to have benefits. In asthmatics, bronchoscopy decreased length of time on mechanical ventilation (20.5 hours vs 10 hours) and decreased PICU (3.4 d vs 3.1 d) but not overall hospital length of stay [9]. This was often related to findings of thick mucus plugs, secretions, and bronchial casts. A case report in an asthmatic described bronchoscopic instillation of admixed acetylcysteine (20%) with albuterol (0.25 mg/mL) which improved peak inspiratory pressures, auto-PEEP and gas exchange as demonstrated by ABG [10]. In this case, a pediatric bronchoscope was advanced and mucolytics instilled to facilitate removal of mucus plugging when conventional asthma therapy failed.

Other special populations to consider bronchoscopy include those with plastic bronchitis and necrotizing tracheobronchitis. In a small series of patients with plastic bronchitis following Fontan procedure, repeated rigid bronchoscopy was often required in combination with mucolytics and ECMO to remove increasingly gelatinous casts in patients with respiratory failure [11]. Two patients with neonatal necrotizing tracheobronchitis underwent ECMO and prolonged bronchoscopies to remove debris [12]. Bronchoscopy in ECLS is expanded upon later in this chapter.

Atelectasis

Atelectasis may be due to mucus plugging, airway compression, or alveolar destruction and collapse. Although not routinely necessary, flexible bronchoscopy can be performed for atelectasis when it is persistent, recurrent, physiologically important or when the etiology is in question. Atelectasis may be improved via flexible bronchoscopy in 45–75% of patients [5, 8] with the etiology of atelectasis identified in 62–100% of cases [1]. Flexible bronchoscopy has been used to relieve atelectasis in pneumonia, cystic fibrosis, hyaline membrane disease, and plastic bronchitis, among other scenarios. Whereas saline is typically used, mucolytics and other agents have been used with varying success.

In a retrospective analysis of 56 cases of unresolved atelectasis in infancy, bronchoscopy led to a revised diagnosis and change in the management of 38 patients (67.8%), including congenital airway abnormalities (46.4%), mucus plugs (28.5%), inflammatory changes (10.7%), hypoplasia (4%), endobronchial granulation tissue (3.5%), and foreign body (3.5%). The most common airway abnormalities were tracheobronchomalacia, laryngomalacia, and various combinations of airway malacia [13].

Given that atelectasis and subsequent ventilation improves with bronchoscopy in a large percentage of neonates, early bronchoscopy has been proposed. Theoretically, decreased mechanical ventilation time could be associated with less subglottic stenosis or chronic lung disease that has been associated with prolonged ventilation.

Most data on bronchoscopy for atelectasis comes from case reports rather than trials [1]. Gans described 50 children in the 1950s with prolonged atelectasis who underwent bronchoscopy [14]. The theory was relief of atelectasis would prevent the development of bronchiectasis. Children with a positive Mantoux skin test were less likely to have resolution than those with a negative skin test. Most cases were related to infection (Tuberculosis, measles and other infections) and bronchoscopic aspiration improved the atelectasis. Abu-Hasan described a 6-year-old with recurrent left lung atelectasis despite being treated for asthma-related respiratory failure with steroids, azithromycin, inhaled mucolytics, bronchodilators, chest physiotherapy, and surfactant [15]. Air insufflation with 50 ml increments totaling 200 ml per lobe through the bronchoscope resulted in lung re-expansion, although notably this was accompanied by suctioning. Krause et al. [16] described 5 children with respiratory failure who received bronchoscopic surfactant for atelectasis. The children had respiratory failure, cultures demonstrating infection, and failed conventional therapy. Radiographs, PaO2/FiO2, and respiratory rates improved. The authors hypothesized direct bronchoscopic instillation-enabled targeted administration, in part reducing the dilution of the surfactant to unaffected areas when administered endotracheally. Case reports

using bronchoscopically administered recombinant human DNAse (2.5 mg in 10 ml saline, for example) have been described in quadriplegia with recurrent atelectasis, cystic fibrosis with persistent atelectasis and others [17, 18], and other conditions, but again comparison studies are lacking. Repeated bronchoscopic lavage with N-acetylcysteine in a 2-month-old with severe respiratory failure from pertussis has also been described [19].

Hemoptysis and Pulmonary Hemorrhage

Chest radiographs are routinely performed in children with hemoptysis. Computerized tomography with contrast may define cavitary lesions or pulmonary arterio-venous malformations. Bronchoscopy can identify potential causes and locations (Fig. 32.2). Hemosiderin-laden macrophages appear 3 days after acute bleeding and remain high for 10 days. Cardiac echo can be considered if these studies are inconclusive, followed by testing for immune-mediated disease. Open lung biopsy is rarely needed [20].

Flexible bronchoscopy may be used to clear clots from the airway and to identify the site of bleeding. A careful, stepwise evaluation of all visualized segments may identify an endobronchial abnormality or identify the lobe or lobes that are the source of the hemoptysis. Significant, active bleeding may require rigid bronchoscopy as visualization and suction with the flexible bronchoscope, particularly the smallest ones, may be compromised. Prior bleeding that has since stopped may be identified by hemosiderin-laden macrophages in the BAL. Diffuse alveolar hemorrhage may be recognized by specimens that become progressively bloodier in the absence of obvious trauma.

Pulmonary hemorrhage may have many etiologies and regional findings may differ, such as those with high volumes of cystic fibrosis or congenital heart disease. Other relatively common causes include infection, foreign-body aspiration, and non-pulmonary causes such as upper airway bleeding and hematemesis [20]. Trauma, cardiac, tumors, pulmonary-renal syndromes, and others are less common. A recent study from India concluded that bleeding was the result of prior infection (Tuberculosis, complicated pneumonia) in 25% of cases, immune-mediated in 18.2%, related to cardiac and vascular disorders in 15.9%, and airway pathologies in 4.5%. Idiopathic pulmonary hemosiderosis, as a diagnosis of exclusion, was made in 36.4% of cases [21]. For idiopathic pulmonary hemosiderosis, the classic triad of hemoptysis, iron deficiency anemia, and pulmonary infiltrates was found in only 56.2%. This study showed a high percentage of patients (91%) had hemosiderin-laden macrophages. A minority (25%) underwent lung biopsies. Steroids were used for IPH and immune-mediated disease whereas interventional radiology performed embolization in those with dilated bronchial arteries due to cardiac causes or post-infectious bronchiectasis. Rarely, surgery was required.

In the ICU, bronchoscopy may help guide intubation if visualization is otherwise difficult.

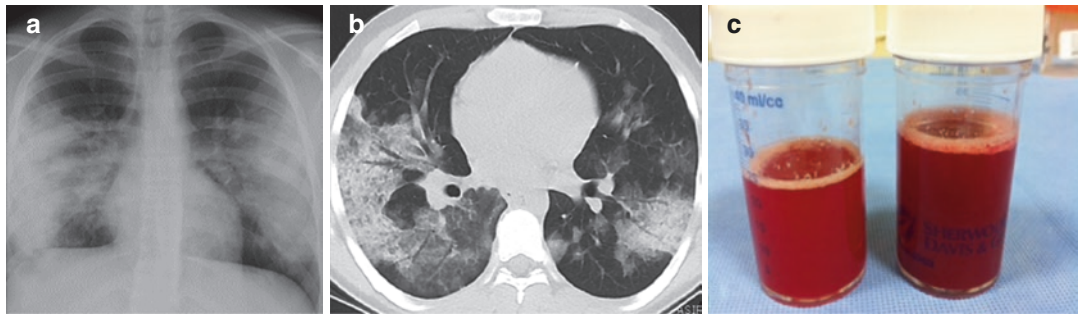

Fig. 32.2 (**a**) Chest X-ray and (**b**) CT in a patient with hemoptysis. (**c**) Bronchosocopy demonstrated progressively bloodier secretion consistent with diffuse alveolar hemorrhage

Placement of the ETT may help prevent aspiration from upper airway, oropharyngeal, and GI causes of bleeding. Bronchoscopy may also be used to place an ETT beyond a bleeding upper airway lesion or to facilitate single-lung ventilation. Occasionally bleeding may be temporized by the instillation of iced saline or lidocaine with epinephrine. Endobronchial lesions that are bleeding may potentially be treated with ablation, including laser, cryotherapy, or argon plasma coagulation. Often considered "interventional procedures," these are discussed elsewhere.

Bronchoscopy in Patients Receiving ECLS

Patients on extracorporeal life support (ECLS) are fully anticoagulated and often have concomitant coagulopathy, platelet dysfunction, and systemic fibrinolysis, raising concern for pulmonary hemorrhage during bronchoscopy. However, prolonged ECLS in and of itself is associated with poor outcomes and bronchoscopy may decrease time spent receiving ECLS. Karlson et al. detected no significant complications during initial investigations of flexible bronchoscopy in children on ECMO [22]. Investigators subsequently theorized more aggressive pulmonary management may shorten ECLS times and that bronchoscopy may be a factor. In a same-hospital historical control study, high-frequency percussive ventilation (HFPV) was combined with therapeutic bronchoscopy in children with respiratory failure requiring ECLS. The children underwent initial bronchoscopy with the goal of mucus removal with subsequent bronchoscopies used until minimal mucus plugs were encountered. Univariate analysis showed the HFPV group underwent more bronchoscopies and experienced more ECLS-free days alive at 30 and 60 days. However, the number of bronchoscopies was not retained as a significant independent predictor of ECLS-free days in stepwise multivariate analysis [23]. Nonetheless, it suggested mode of mechanical ventilation and pulmonary toilet strategy were modifiable factors that affect the duration of extracorporeal support. Preweaning bronchoscopy was suggested to reduce weaning failures in patients undergoing veno-arterial ECMO [24].

In the meta-analysis previously described [5], four studies reported yield in 174 patients receiving ECLS. FFB was successfully used to re-expand collapsed lobes in 42.9% of patients. Repeat therapeutic lavage was associated with increased lung expansion, improved tidal volumes, improved lung recruitment, and decreased ventilator support, ultimately reducing ECLS support and separation from ECLS.

Notably, common clinical signs of infection may be obscured in patients undergoing ECLS. This is in part due to control of body temperature by the ECLS circuit and the systemic inflammatory response induced by ECLS. A high index of suspicion is required in patients with new infiltrates or failure to wean from ECLS support. Investigators recommended consideration of early and repeat bronchoscopy in patients receiving ECLS support. If able to improve respiratory mechanics and thus the need for ECLS, it has been postulated that flexible bronchoscopy could "decrease morbidity and mortality associated with prolonged ACLS support" [5].

A retrospective study of 79 children on ECMO underwent 153 total flexible bronchoscopies. Indications included tenacious airway secretions (77%) or evaluation of suspected secondary infections (17%) in most patients. There was no deterioration of radiographic findings after the procedure, nor were there significant changes in heart rate, systemic blood pressure or temperature. Furthermore, there was no significant change in ECMO pump flow rate or sweep gas flow during or after bronchoscopy [25].

Bleeding has been described in 15.9% of procedures, likely related to systemic anticoagulation required during ECLS. This was typically easily controlled. Local trauma (pneumothorax, perforation) (0.2% of 5060), stridor (0.3%), bronchospasm (0.5%), and fever (4.1%) were also noted [5].

Adverse Events During Bronchoscopy in the ICU

Flexible bronchoscopy and BAL are associated with minor "consequences" and known complications. These include but are not limited to epistaxis or other bleeding, laryngo- or bronchospasm, atelectasis, infection, fever, arrhythmias, and death [1]. In the ICU setting, the physiologic effects of bronchoscopy may have more consequences than in the ambulatory setting.

Adverse events were reported in 16 studies of those examined in the meta-analysis described in this chapter (5060 bronchoscopies) [5]. The most common adverse events were hypoxia, bradycardia, hypotension, and bleeding. Hypoxia was reported in 2.3% of cases, typically resolving with the removal of the bronchoscope and/or supplemental oxygen. Bag-mask ventilation was required in 6.1% of patients with hypoxia. Bradycardia was reported in 0.4% of patients with hypoxia, and one study showed 3.4% of these patients required atropine [26]. Hypotension occurred in 1.2% and typically responded to a fluid bolus. Bleeding occurred in 4% of procedures in usually resolved spontaneously. A minority required saline or epinephrine lavage for bleeding cessation. The rate of bleeding was higher in patients receiving ECLS. Three patients who received fentanyl developed rigid chest, among the most serious complications noted. Two deaths were reported, both in neonates with full thickness necrotizing tracheobronchitis and mainstem perforation [27]. The patients at highest risk for complications included immunocompromised and those receiving ECLS [5].

Notably, anesthesia is one of the most significant complications of pediatric flexible bronchoscopy. As such, it is recommended that sedating and monitoring the patient should be separate from the responsibility of performing endoscopy, implicating the essential role of an anesthesiologist or sedating physician.

Summary

When considering bronchoscopy in the NICU and PICU, one must recognize the potential physiologic consequences of the procedure to maximize safety in this sick population. Bronchoscopy may identify anatomic abnormalities, guide treatment decisions, and be useful for various diagnostic and therapeutic scenarios. Special populations likely to benefit from early bronchoscopy include neonates, those receiving ECLS, those with congenital anomalies such as heart disease, and the immunocompromised. This chapter has also focused on the use of bronchoscopy in patients with atelectasis and hemoptysis. Flexible bronchoscopy has great utility in critically ill children.

References

1. Faro A, Wood RE, Schechter MS, Leong AB, Wittkugel E, Abode K, et al. Official American Thoracic Society technical standards: flexible airway endoscopy in children. Am J Respir Crit Care Med. 2015;191(9):1066–80.
2. Linnane B, Hafen GM, Ranganathan SC. Diameter of paediatric sized flexible bronchoscopes: when size matters. Pediatr Pulmonol. 2006;41(8):787–9.
3. Koumbourlis AC. Flexible fibre-optic bronchoscopy in the intensive-care unit. In: Priftis KN, Anthracopoulos MB, Eber E, Koumbourlis AC, Wood RE, editors. Paediatric bronchoscopy, vol. 38: Karger; 2010. p. 54–63.
4. Wood RE. Bronchoscopy in the pediatric intensive care unit. In: Wheeler DS, Wong HR, Shanley TP, editors. The respiratory tract in pediatric critical illness and injury. London: Springer; 2009.
5. Field-Ridley A, Sethi V, Murthi S, Nandalike K, Li ST. Utility of flexible fiberoptic bronchoscopy for critically ill pediatric patients: a systematic review. World J Crit Care Med. 2015;4(1):77–88.
6. Hsia D, DiBlasi RM, Richardson P, Crotwell D, Debley J, Carter E. The effects of flexible bronchoscopy on mechanical ventilation in a pediatric lung model. Chest. 2009;135(1):33–40.
7. Bar-Zohar D, Sivan Y. The yield of flexible fiberoptic bronchoscopy in pediatric intensive care patients. Chest. 2004;126(4):1353–9.

8. Kohelet D, Arbel E, Shinwell ES. Flexible fiberoptic bronchoscopy--a bedside technique for neonatologists. J Matern Fetal Neonatal Med. 2011;24(3):531–5.
9. Maggi JC, Nussbaum E, Babbitt C, Maggi FE, Randhawa I. Pediatric fiberoptic bronchoscopy as adjunctive therapy in acute asthma with respiratory failure. Pediatr Pulmonol. 2012;47(12):1180–4.
10. Henke CA, Hertz M, Gustafson P. Combined bronchoscopy and mucolytic therapy for patients with severe refractory status asthmaticus on mechanical ventilation: a case report and review of the literature. Crit Care Med. 1994;22(11):1880–3.
11. Preciado D, Verghese S, Choi S. Aggressive bronchoscopic management of plastic bronchitis. Int J Pediatr Otorhinolaryngol. 2010;74(7):820–2.
12. Michael EJ, Zwillenberg D, Furnari A, Sheppard L, Desai HJ, Wolfson PJ, et al. Treatment of neonatal necrotizing tracheobronchitis with extracorporeal membrane oxygenation and bronchoscopy. J Pediatr Surg. 1988;23(9):798–801.
13. Vijayasekaran D, Gowrishankar NC, Nedunchelian K, Suresh S. Fiberoptic bronchoscopy in unresolved atelectasis in infants. Indian Pediatr. 2010;47(7):611–3.
14. Gans B. Bronchoscopic treatment of atelectasis in children. Arch Dis Child. 1952;27(133):254–6.
15. Abu-Hasan MN, Chesrown SE, Jantz MA. Successful use of bronchoscopic lung insufflation to treat left lung atelectasis. Pediatr Pulmonol. 2013;48(3):306–9.
16. Krause MF, von Bismarck P, Oppermann HC, Ankermann T. Bronchoscopic surfactant administration in pediatric patients with persistent lobar atelectasis. Respiration. 2008;75(1):100–4.
17. Slattery DM, Waltz DA, Denham B, O'Mahony M, Greally P. Bronchoscopically administered recombinant human DNase for lobar atelectasis in cystic fibrosis. Pediatr Pulmonol. 2001;31(5):383–8.
18. McLaughlin AM, McGrath E, Barry R, Egan JJ, Gallagher CG. Treatment of lobar atelectasis with bronchoscopically administered recombinant human deoxyribonuclease in cystic fibrosis? Clin Respir J. 2008;2(2):123–6.
19. Mata AF, Sarnaik AA. Bronchoscopy with N-acetylcysteine lavage in severe respiratory failure from pertussis infection. Pediatrics. 2013;132(5):e1418–23.
20. Godfrey S. Pulmonary hemorrhage/hemoptysis in children. Pediatr Pulmonol. 2004;37(6):476–84.
21. de Silva C, Mukherjee A, Jat KR, Lodha R, Kabra SK. Pulmonary hemorrhage in children: etiology, clinical profile and outcome. Indian J Pediatr. 2018;86(1):7–11.
22. Karlson KH Jr, Pickert CB, Schexnayder SM, Heulitt MJ. Flexible fiberoptic bronchoscopy in children on extracorporeal membrane oxygenation. Pediatr Pulmonol. 1993;16(4):215–8.
23. Yehya N, Dominick CL, Connelly JT, Davis DH, Minneci PC, Deans KJ, et al. High-frequency percussive ventilation and bronchoscopy during extracorporeal life support in children. ASAIO J. 2014;60(4):424–8.
24. Luedi M, Friess JO, Erdoes G, Veno-Arterial ECMO. Weaning failure in the operating room: have you considered Preweaning bronchoscopy? Artif Organs. 2018;42(12):1234–35.
25. Kamat PP, Popler J, Davis J, Leong T, Piland SC, Simon D, et al. Use of flexible bronchoscopy in pediatric patients receiving extracorporeal membrane oxygenation (ECMO) support. Pediatr Pulmonol. 2011;46(11):1108–13.
26. Efrati O, Sadeh-Gornik U, Modan-Moses D, Barak A, Szeinberg A, Vardi A, et al. Flexible bronchoscopy and bronchoalveolar lavage in pediatric patients with lung disease. Pediatr Crit Care Med. 2009;10(1):80–4.
27. Pietsch JB, Nagaraj HS, Groff DB, Yacoub UA, Roberts JL. Necrotizing tracheobronchitis: a new indication for emergency bronchoscopy in the neonate. J Pediatr Surg. 1985;20(4):391–3.

Endobronchial Biopsy (in Children with Severe Uncontrolled Asthma)

33

Mikhail Kazachkov

Safety of Endobronchial Biopsy in Pediatrics

Despite anxiety, expressed by some practitioners, endobronchial biopsy in children is a very safe procedure as it was reported by Bush and Pohunek in 2000, after analysis of 34 unpublished cases [1]. Saglani et al. [2] showed that endobronchial biopsy did not increase complication rate in 33 children when compared to 33 controls, who underwent flexible bronchoscopy without biopsy. Quite reassuring safety data was obtained by Salva et al. on 170 pediatric patients, neither of whom had pneumothorax, pneumonia, respiratory distress, hemoptysis or even considerable mucosal bleeding, or any other complication after bronchoscopy with endobronchial biopsy procedures [3]. The authors reported an average procedure length of 12 min with a recovery time of 90 min. Of note, 39 patients had severe asthma, and 29 were less than 5 years old.

Instruments

Flexible biopsy forceps (FBF) are the best tool for performing endobronchial biopsy in pediatrics. Most operators use 1.0 and 2.0 mm diameter disposable forceps. There are also 1.5 mm forceps now available (FB 433D), which could be used with Olympus Bf-MP190 bronchoscope with 1.7 mm operating channel. It was shown that the use of 2.0 mm biopsy forceps rather than the 1.0 mm significantly reduced biopsy time, 4.6 (2.5–9.0) min versus 8.4 (4.4–16.6) min, $p < 0.001$ [4]. There is no data on the efficiency of 1.5 mm forceps; however, it is the author's personal experience that the samples obtained with them are inferior in quality to the ones obtained with 2.0 mm forceps.

For choosing appropriately sized forceps depending on the size of the operating channel of the bronchoscope, please refer to Table 33.1.

There is no consensus regarding the amount of endobronchial biopsy samples, which need to be obtained from the patient in order to yield adequate diagnostic results. In one study, 121 biopsy specimens were taken from 69 subjects (average 1.75 samples per patient), and at least one specimen was suitable for assessment for all except one subject [5], which correlates with the author's experience as well.

Electronic Supplementary Material: The online version of this chapter (https://doi.org/10.1007/978-3-030-54924-4_33) contains supplementary material, which is available to authorized users.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_33

Table 33.1 Olympus flexible endobronchial biopsy forceps and bronchoscope channel sizes

Product description	Product codes	Scope channel	Cup opening size
Disposable EndoJaw	FB-211D.A/221D.A/231D.A/241D.A	2.0 mm	5.0 mm
Reusable Biopsy Forceps	FB-35C-1/55CR-1	2.8 mm	7.3 mm
Reusable Biopsy Forceps	FB-20C-1/22C-1	2.6 mm	5.0 mm
Reusable Biopsy Forceps	FB-19C-1/19CR-1/34C-1/21C-1/15C-1/52C-1	2.0 mm	Multiple (please refer to catalog)
Reusable Biopsy Forceps	FB-433D	1.7 mm	Information is not available
Reusable Biopsy Forceps	FB-56D-1	1.2 mm	7.3 mm

Adapted from www.olympusamerica.com

Endobronchial Biopsy Techniques

Traditional Technique

(a) Perform careful airway inspection, and choose the endobronchial biopsy site. Middle lobe sub-carina is often preferred due to its easy accessibility; however, with proper experience and technique, endobronchial biopsy could be taken from multiple other airway sites.

(b) Carefully suction airway secretions making sure that you achieve an unobstructed view of the biopsy site.

(c) Withdraw the bronchoscope and suction normal saline (NS) via the bronchoscope channel until the suction tubing is clear. This avoids obstruction of the view with thick airway secretions or blood, which could be "pushed" through the channel during passage of the FBF.

(d) Attach oxygen (O_2) to the bronchoscope, and insufflate 1–2 L/min for 5–10 s while submerging the tip of the bronchoscope in a bucket of water or NS to dry out the channel. This helps avoid "bubbling" at the tip of the bronchoscope, which may occur during passage of the FBF if the channel is filled with NS from suctioning.

(e) Introduce bronchoscope into the airway while performing continuous (during passage through upper airway) and intermittent (during passage through lower airway) insufflation with 1–2 L/min of O_2. Once again, this technique helps avoid plugging of the channel of the bronchoscope with thick respiratory secretions, which subsequently could be pushed forward during passage of the FBF obstructing the view of the biopsy site.

(f) Position the bronchoscope so that you have a clear and unobstructed view of the chosen biopsy site. Avoid bending or rotating the bronchoscope, and adjust the height of the bed so that you are comfortable with handling the shaft of the bronchoscope in a completely erect position. Do not bend the tip of the bronchoscope, and remain in neutral position maintaining a clear view of the biopsy site.

(g) Instruct the bronchoscopy assistant to introduce the FBF in a smooth, slow motion. Forcing passage of the FBF against resistance is prohibited, as it will ultimately damage the bronchoscope.

(h) Small bubbles of fluid usually appear at the tip of the bronchoscope when the FBF approach the exit. Instruct assistant to advance even slower.

(i) The tip of the FBF will appear just past the tip of the bronchoscope. At this point instruct assistant to stop advancing while you adjust the position of the bronchoscope so that the tip of the forceps aim directly at the chosen biopsy site.

(j) Instruct assistant to slowly advance the FBF until the tip of the forceps is pointing directly at the chosen biopsy site and is located in the closest possible proximity to it.

(k) Instruct assistant to open the forceps. In the ideal situation, the jaws of the forceps should be angled close to 90° at the chosen sub-

carina, which facilitates "grabbing." However, in many cases, positioning is not optimal, and you would have to turn the shaft of the bronchoscope together with the FBF to achieve the proper "grabbing" angle.

(l) Instruct assistant to advance the open FBF slowly until the sub-carina is located inside the jaws of the forceps, and the assistant reports feeling resistance to further advancement.

(m) Instruct assistant to close the forceps while maintaining resistance. Observe the FBF "biting" the sub-carina.

(n) Pull the bronchoscope back approximately 2 cm and make sure that the bronchoscope is not bent to avoid damage to the tip during rapid pullback of the FBF.

(o) Instruct assistant to pull the FBF. The pulling motion should be abrupt but short to avoid rapid backward passage of the FBF through the tip of the bronchoscope and its subsequent damage.

(p) Instruct assistant to pull the FBF all the way out of the channel while keeping the forceps in a closed position. Assistant then flushes the biopsy specimen into the proper media solution.

(q) Check the biopsy site for excessive bleeding.

(r) If another sample is to be obtained, FBF should be rinsed with NS to avoid introducing media solution into the channel of bronchoscope and the airway.

"Parallel" Technique

This is the alternative endobronchial biopsy technique developed by the author. Its principal lays in introduction of the FBF not through the bronchoscope channel but rather "in parallel" to the bronchoscope, which allows utilization of 2 mm FBF alongside smaller pediatric bronchoscopes with 1.2 mm channel. The technique is particularly helpful in smaller children and babies when manipulation of the airway with a large diameter bronchoscope is undesirable.

(a) Perform careful airway inspection, and choose the endobronchial biopsy site; suctioning secretions so that you obtain an unobstructed view of the chosen biopsy site.

(b) Perform direct laryngoscopy with properly sized laryngoscope. Obtain a good view of the glottis.

(c) Carefully introduce 2 mm FBF in the glottis so that the tip of the forceps is positioned just below the vocal cords. Avoid "blind" introduction of the FBF deeper into the airway.

(d) Hand the FBF to bronchoscopy assistant.

(e) You may carefully remove laryngoscope.

(f) Introduce the bronchoscope via the nostril, and after passing the vocal cords, locate the tip of the FBF, which should be positioned in the upper trachea.

(g) Instruct the bronchoscopy assistant to slowly and carefully advance the FBF further down the trachea. Assure good visualization of the tip of the FBF with the bronchoscope during this maneuver.

(h) Facilitate introduction of FBF into right or left main bronchus by turning the head of the patient to the opposite direction (turn head to the left to get in the right main bronchus, or turn head to the right to get in the left main bronchus). Instruct assistant to slowly advance FBF further without losing sight of the tip of the forceps.

(i) Under direct visualization with the bronchoscope, position the tip of the FBF in the closest possible proximity to the chosen biopsy site pointing directly at the sub-carina.

(j) Instruct assistant to open the forceps. Once again, in the ideal situation, the jaws of the forceps should be angled close to 90° at the chosen sub-carina, which facilitates "grabbing." However, in many cases, positioning is not optimal, and you would have to instruct the assistant to rotate the forceps until the proper angle is achieved. This can be accomplished by rolling the proximal shaft of the FBF between the thumb and index finger clockwise or counterclockwise.

(k) Instruct assistant to slowly advance the open FBF until the sub-carina is located inside the jaws of the forceps, and the assistant reports feeling resistance to further advancement.
(l) Instruct assistant to close the forceps while maintaining resistance. Observe the FBF "biting" the sub-carina.
(m) Pull the bronchoscope back in order to avoid damage to the tip during rapid pullback of the FBF.
(n) Instruct assistant to pull the FBF all the way out of the channel while keeping the forceps in a closed position. Assistant then flushes the biopsy specimen into the proper media solution.
(o) Check the biopsy site for excessive bleeding.
(p) If another sample is to be obtained, FBF should be rinsed with NS to avoid introducing media solution into the airway.

Of note, "parallel" technique can be successfully used in tracheostomy patients. The preferred method is to guide the bronchoscope via the nose or mouth alongside tracheostomy tube while the FBF are introduced via tracheostomy tube into lower trachea and easily visualized via bronchoscope there and subsequently guided into desired biopsy site under direct visualization with the bronchoscope.

Sample Processing and Anatomic Pathology Report[1]

Sample processing depends on institutional protocols. Most commonly, the obtained biopsy specimens are placed in formalin and subsequently cut and stained with hematoxylin and eosin (H&E) or another stain to assess the quality and adequate morphology, as well as the presence and quantity of inflammatory cells in the submucosa and thickness of the reticular basement membrane (RBM). In children with severe uncontrolled asthma (SUA), several important histological characteristics of endobronchial biopsy specimens have to be included in the anatomic pathology report.

Predominant Inflammatory Cells

Most patients with severe uncontrolled asthma have strong predominance of lymphoplasmocytic cells in the lamina propria [6]. This pattern seems to be not specific for asthma and is present in children with cystic fibrosis who also have strong predominance of lymphocytes in their subepithelial bronchial tissue even in the presence of severe BAL neutrophilia [7]. Neutrophilic infiltrates in bronchial submucosa were reported in 36% of patients with SUA, and their presence did not correlate with BAL neutrophilia [6]. Finally, eosinophilic infiltrates are found in many patients with persistent airway eosinophilia phenotype of SUA. Of note, both neutrophilic and eosinophilic infiltrates may be present in patients with a predominance of lymphoplasmocytic cells in bronchial wall biopsy.

Assessment of Eosinophils in Biopsy Sample

There are two principal methods of assessing eosinophils in endobronchial biopsy samples.

First method is based on calculating the number of eosinophils per high-power field, or alternatively in tissue section [8]. The benefit of this method is its simplicity and availability in most medical institutions. Second method utilizes immunostaining techniques and has the advantage of a more accurate quantitative assessment of tissue eosinophils alongside other inflammatory cells [9]. Apparently, the latter method is mostly used in research settings and may not be readily available for daily clinical use.

[1]For advanced description of assessment of endobronchial eosinophils and RBM thickness and their role in phenotyping of SUA, please see the Chap. 24.

Reticular Basement Membrane Thickness

There are many different methods of measuring RBM thickness. The easiest method is based on the pathologist's impression. Despite the fact that this assessment is subjective and merely qualitative, it was shown to be useful in clinical practice and, in the author's opinion, can be utilized as a research tool as well [6]. More sophisticated qualitative methods of measurement of RBM thickness were described elsewhere and were successfully used by researchers previously [10].

In conclusion, endobronchial biopsy is a safe, relatively simple, and extremely informative method of assessing lower airway inflammation and airway remodeling in patients with SUA. Its proper utilization allows for bronchoscopic phenotyping of SUA and for developing individualized treatment plans.

References

1. Bush A, Pohunek P. Brush biopsy and mucosal biopsy. Am J Respir Crit Care Med. 2000;162(2) Pt 2:S18–22.
2. Saglani S, Payne DN, Nicholson AG, Scallan M, Haxby E, Bush A. The safety and quality of endobronchial biopsy in children under five years old. Thorax. 2003;58(12):1053–7.
3. Salva PS, Theroux C, Schwartz D. Safety of endobronchial biopsy in 170 children with chronic respiratory symptoms. Thorax. 2003;58(12):1058–60.
4. Regamey N, Balfour-Lynn I, Rosenthal M, Hogg C, Bush A, Davies JC. Time required to obtain endobronchial biopsies in children during fiberoptic bronchoscopy. Pediatr Pulmonol. 2009;44(1):76–9.
5. Bossley CJ, Fleming L, Gupta A, Regamey N, Frith J, Oates T, et al. Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. J Allergy Clin Immunol. 2012;129(4):974–82. e13.
6. Erkman J, Vaynblat A, Thomas K, Segal LN, Levine J, Moy L, et al. Airway and esophageal eosinophils in children with severe uncontrolled asthma. Pediatr Pulmonol. 2018;53(12):1598–603.
7. Regamey N, Tsartsali L, Hilliard TN, Fuchs O, Tan HL, Zhu J, et al. Distinct patterns of inflammation in the airway lumen and bronchial mucosa of children with cystic fibrosis. Thorax. 2012;67(2):164–70.
8. Sullivan P, Stephens D, Ansari T, Costello J, Jeffery P. Variation in the measurements of basement membrane thickness and inflammatory cell number in bronchial biopsies. Eur Respir J. 1998;12(4):811–5.
9. Balzar S, Wenzel SE, Chu HW. Transbronchial biopsy as a tool to evaluate small airways in asthma. Eur Respir J. 2002;20(2):254–9.
10. van Mastrigt E, Vanlaeken L, Heida F, Caudri D, de Jongste JC, Timens W, et al. The clinical utility of reticular basement membrane thickness measurements in asthmatic children. J Asthma. 2015;52(9):926–30.

Transbronchial Biopsy

34

Levent Midyat and Gary Visner

Introduction

Lung biopsy is required for appropriate diagnosis and management of a variety of pulmonary diseases. There are currently multiple different ways of obtaining the tissue samples including transbronchial biopsy (TBB), endobronchial biopsy, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), computerized tomography-guided fine needle aspiration (CT-FNA), and video-assisted thoracoscopic surgery or open lung biopsy.

Transbronchial biopsy was first performed by Andersen et al. in 1965 by using a rigid bronchoscope [1, 2]. Although the initial results were promising, there was a high incidence of pneumothorax [3]. In 1974, Levin et al. published their experience with TBB using flexible bronchoscopy which resulted in obtaining a histological diagnosis in most of the cases with no serious complications [4, 5]. A technique of attaching a plastic suction catheter to a neonatal bronchoscope (2.2 mm in diameter with no working channel) was described by Mullins et al. in 1995 [6]. This was followed by the development of a small flexible biopsy forceps that could fit through the 1.2 mm working channel of the pediatric flexible fiber-optic bronchoscope which aroused further interest in the technique since a diagnostic TBB could obviate the need for an open lung biopsy [7]. Advances in technology and biopsy techniques over the past two decades have led to improved yields with fewer complications in the pediatric population.

Indications

TBB may be performed to obtain a tissue diagnosis for conditions such as lung transplantation, tumors, inflammatory diseases, infections, and interstitial lung diseases. The overall diagnostic yield for specific diagnosis varies widely, depending on the size, location, and extent of lung infiltrates and the nature of underlying lung disease. Even though TBB provides adequate lung specimen in the majority of cases, a specific diagnosis could not be rendered in a significant proportion of the patients. Nonspecific findings on TBB are often not helpful and can lead to erroneous clinical decisions [8]. Pulmonary disorders in which a diagnosis is possible with TBB are listed in Table 34.1.

Lung Transplantation

Early recognition and targeted therapy of complications after lung transplantation are critical

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_34

Table 34.1 Possible indications for transbronchial biopsy

Acute lung transplant rejection
Infections
Pneumocystis pneumonia
Fungal infections
Viral infections
Tuberculosis
Non-tubercular mycobacterial infections
Diffuse lung diseases
Sarcoidosis
Lymphangitic carcinomatosis
Pulmonary alveolar proteinosis
Pulmonary Langerhans cell histiocytosis
Eosinophilic pneumonia
Lipoid pneumonia
Drug-induced pneumonitis
Alveolar microlithiasis
Amyloidosis
Lymphangioleiomyomatosis
Bronchiolitis obliterans with organizing pneumonia
Neoplastic pulmonary disorders

to long-term survival. With increased utilization of lung transplantation in the pediatric population, TBB in children has become the standard practice to monitor the lung allograft after transplantation, either as surveillance or clinically indicated procedure in the diagnosis of allograft rejection. TBB has a sensitivity and specificity of 94% and 90%, respectively, for suspected acute allograft rejection [9]. Several studies have found surveillance bronchoscopy with TBB to be a high-yield procedure; however, some others have found no benefits of surveillance bronchoscopy and TBB in lung transplant recipients [8].

There is no current consensus regarding the frequency of surveillance TBB in pediatric transplant recipients. More TBB are usually performed in the first year after transplant due to the higher rate of acute rejection and infection during this time period. Furthermore, determining appropriate criteria for the adequacy of TBB sampling is a significant challenge in children, particularly infants, due to the size of both the patient and the equipment used to collect tissue specimens [10]. At least five pieces of well-expanded alveolated parenchyma are recommended for adequate morphologic evaluation of a transbronchial lung allograft biopsy specimen for acute rejection. To ensure that these recommendations are fulfilled, the bronchoscopist may need to sample more than five pieces [11, 12]. The current ISHLT classification for acute rejection includes the presence and severity of perivascular and interstitial mononuclear infiltrates (grade A0–A4) and the presence and severity of small airways inflammation or lymphocytic bronchiolitis (grade B0–2) [12, 13].

According to an older pediatric study, 25% of TBBs performed in lung transplant recipients were undertaken for surveillance, 38% for follow-up of acute rejection, and 37% for respiratory symptoms, and a treatable grade of acute rejection was found in 24% of the surveillance procedures [7]. This study also showed that only 5% of the surveillance TBBs performed with pediatric forceps demonstrated acute rejection compared to 29% of the biopsies performed with adult forceps, the confounder being that the pediatric forceps were used in the younger patients, where the incidence of acute rejection is lower. The data suggested that this procedure was successful in obtaining tissue for pathologic diagnosis in 85% of patients and was relatively safe with a serious complication rate of only 2% [7, 12–14]. Many other studies reported that surveillance transbronchial biopsies showed histological features of rejection or infection in 19–57% of procedures [15–18]. In contrast, some studies reported no acute rejection episode needing therapeutic intervention with true surveillance bronchoscopy [9].

TBB has low sensitivity for detecting bronchiolitis obliterans; however, fiber-optic bronchoscopy with TBB could be helpful in these patients to evaluate for airway complications, lung infections, and acute graft rejection, which is an established risk factor for developing bronchiolitis obliterans. The clinical reasons for performing bronchoscopy with TBB are >10% decline in FEV1, >20% decline in FEF25–75, radiographic infiltrates, clinical suspicion for infection, and symptoms referable to respiratory tract [8].

Lung Infections

Although most pulmonary infections can be diagnosed by performing bronchoalveolar lavage and brushing, TBB increases the diagnostic yield and rules out noninfectious causes in some cases. TBB might be indicated in the diagnosis of nonresolving pneumonia, smear-negative pulmonary tuberculosis, non-tubercular mycobacterial (NTM) infections, fungal infections, viral processes, and immunocompromised status with lung infiltrates. In particular, TBB increases the diagnostic yield for *Pneumocystis jiroveci (carinii)* pneumonia in patients with neoplastic disorders, bone marrow transplant recipients, acquired immunodeficiency syndromes, and those receiving immunosuppressive medications [19–21].

Even though TBB provides diagnostic information in 15–68% of immunosuppressed patients with pulmonary infiltrates, nonspecific inflammatory/fibrotic findings and possible procedure-related complications, especially in those who are critically ill and have associated comorbid conditions, limit the utility of TBB in these patients [8]. Surgical lung biopsies might be performed if needed to make the diagnosis of either noninfectious or infectious causes of lung infiltrates in this population. Bronchial washing and BAL are the most valuable bronchoscopic procedures for the diagnosis of pulmonary fungal infections and viral infections such as adenovirus or CMV pneumonitis, and TBB adds only a modest improvement in diagnostic yield in these patients [22, 23].

TBB provides the appropriate sampling particularly in the diagnosis of tuberculosis and respiratory bronchiolitis in which the involvement of the disease is apparent in the center of or around the bronchioles [24, 25]. In addition to providing rapid diagnosis in miliary tuberculosis, TBB also provides rapid diagnosis in 17–60% of cases with confirmed active tuberculosis and is the exclusive source of diagnostic specimen in 10–20% of these patients [26–31].

The possible presence of non-tuberculous mycobacteria (NTM) lung disease often arises clinically when NTM are identified on sputum culture from a patient under evaluation for tuberculosis. However, differentiating a contamination or colonization from a true NTM infection could be difficult at times. In symptomatic patients with evidence of pulmonary disease by imaging studies and with other processes such as fungal disease, malignancy, and tuberculosis excluded, the American Thoracic Society/Infectious Disease Society diagnostic criteria to support NTM clinical infection as opposed to colonization of secretions include one of the following: (1) positive culture results from at least two separate sputum samples (regardless of AFB smear result), (2) positive culture results from at least one bronchial wash or lavage (regardless of AFB smear result), (3) transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM, (4) biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM, or (5) a positive culture from pleural fluid or any other normally sterile extrapulmonary site [32]. Based on this guideline, TBB should be performed whenever bronchoscopy is needed in patients suspected to have NTM infection.

Diffuse Lung Diseases

Diffuse lung diseases constitute a heterogeneous group of diseases with similar clinical, radiological, and pulmonary function profiles. The diagnostic approach to ILDs complex and histopathological evaluation and immunohistochemical studies of samples obtained by TBB can be used in patients suspected diffuse lung diseases. Although surgical biopsy is the gold standard for the diagnosis of diffuse lung diseases, it is performed in only 12% of cases, whereas TBB is performed in 28% of adult patients because of the lower rates of morbidity and mortality than those associated with surgical biopsy [33, 34].

TBB provides more information in the diagnosis of the diseases that are apparent in the center

of or around the bronchioles, such as hypersensitivity pneumonitis, eosinophilic pneumonia, tuberculosis, and bronchiolitis, and that have involvement throughout the lymphatic distribution, such as sarcoidosis and lymphangitis carcinomatosa. The sensitivity of TBB for sarcoidosis ranges from 50% to 85% in stage 1 disease and is higher if the parenchyma is involved. At least four to six biopsies are required for optimal diagnosis of sarcoidosis [35]. Endobronchial biopsies increase the diagnostic yield by as much as 20% if combined with TBB since bronchial mucosa is frequently involved in sarcoidosis [36, 37]. TBB biopsy is highly sensitive in diagnosing pulmonary alveolar proteinosis, Langerhans cell histiocytosis, eosinophilic pneumonia, lipoid pneumonia, drug-induced pneumonitis, and miscellaneous lung disease [21].

TBB is reported to provide adequate specimen in some cases of diffuse pulmonary amyloidosis, pulmonary alveolar microlithiasis, cryptogenic organizing pneumonia, and acute and subacute hypersensitivity pneumonitis [38, 39]. However, absence of typical histological features on TBB should not be considered conclusive because of the patchy distribution, and surgical biopsy should be performed for further evaluation. TBB may not be reliable for heterogeneous lung diseases such as usual interstitial pneumonia, and low-magnification architectural overview is essential for diagnosis of some diffuse lung diseases such as idiopathic pulmonary fibrosis [8, 40, 41].

Neoplastic Pulmonary Disorders

TBB is commonly used to determine the etiology of lung nodules and masses, especially in the adult population. Although TBB is the most useful sampling method for the diagnosis of peripheral lung cancer with an average diagnostic yield of 57%, usually a combination of sampling procedures such as bronchoalveolar lavage, bronchial brush, TBB, and peripheral TBNA is performed in these patients to maximize the diagnostic yield [42].

The size of the lesion is the most important factor affecting the sensitivity of bronchoscopy for diagnosis of peripheral lung cancers [43]. TBB's diagnostic accuracy increases when the nodule is larger than 2 cm, when the presence of a bronchus leading to the nodule is found on CT of the chest (positive bronchus sign), and when the tissue is repeatedly sampled. Based on the previous studies, 6–10 TBB should be obtained in these patients for an optimal diagnostic yield [1, 8, 35]. The yield of TBB is also high in bronchoalveolar carcinoma and lymphangitic spread of the tumor [21]. The data on usefulness of TBB in pediatric lung cancers and metastatic pulmonary tumors is very limited and mostly anecdotal.

Contraindications

Absolute contraindications for TBB include medical instability, severe hypoxia, status asthmaticus, lack of patient cooperation, malignant arrhythmia, active myocardial ischemia, massive hemoptysis, and uncorrectable bleeding diathesis [21]. Relative contraindications are listed in Table 34.2.

Preparation

For lung transplant non-surveillance transbronchial biopsies, a detailed history, physical examination, and radiological images (chest X-ray and/or computed tomography) are essential before performing the procedure for predicting the yield of TBB on the basis of the anatomic distribution and appearance of any abnormalities. Complete blood counts, coagulation profile, blood chemistry, arterial blood gas analysis, pulmonary function tests, and electrocardiogram are not routinely required prior to the procedure. The purpose, risks, and the limitations of TBB should be thoroughly discussed with the patient and/or the caregivers before the procedure [8, 21].

Transbronchial lung biopsy must be performed in a well-equipped room with facilities

Table 34.2 Relative contraindications for transbronchial biopsy [21]

Conditions	Recommendations
Thrombocytopenia	Use caution when the platelet count is less than 50,000/μL
Coagulopathy	May need administration of vitamin K and fresh frozen plasma
Uremia[a]	Serum creatinine should be measured when renal insufficiency is suspected. A danger of serious hemorrhage exists, even in the presence of normal coagulation parameters; biopsies may be done carefully, preferably soon after dialysis or administration of desmopressin and cryoprecipitate
Pulmonary hypertension[a]	The British Thoracic Society suggests that TBB should be performed with caution in patients with elevated pulmonary arterial pressures
Risk of arrhythmia	Oxygen supplementation to keep the blood oxygen saturation above 90% and thereby minimize the risk of cardiac arrhythmia during and after bronchoscopy
Medications	Low-dose aspirin can be continued if indicated, but clopidogrel is discontinued at least 5 days before the procedure; the BTS recommends discontinuing warfarin 3 days before the procedure and suggests that an international normalized ratio (INR) lower than 1.5 is safe; heparin is discontinued 6 h before the procedure; therapeutically dosed enoxaparin is discontinued 24 h beforehand, whereas enoxaparin given for prophylaxis of deep vein thrombosis prophylaxis is discontinued on the morning of the procedure

[a]Considered as an absolute contraindication in some centers

for monitoring blood pressure, oxygen saturation, heart rate, respiratory rate, and possibly end-tidal CO_2. A flexible bronchoscope, a light source, video monitoring equipment, a biopsy forceps, specimen containers, equipment for cardiopulmonary resuscitation, a suction apparatus, and supplemental oxygen are necessary for performing TBB. TBB is usually performed with the patient in the supine position. Although the majority of the pediatric cases are performed in the operating room under general anesthesia, the procedure could also be done under procedural sedation and anesthesia induced by intravenous opioids and benzodiazepines [21].

There are different sizes and types of single-use or reusable biopsy forceps in the market. Three common types are (1) cup forceps, (2) alligator (toothed) forceps, and (3) forceps with an impaler needle. The alligator forceps and the cup forceps are the most commonly used ones. Alligator forceps tend to provide larger lung tissue specimen than cup forceps of comparable size. The smallest biopsy forceps are compatible with a 1.2 mm instrument channel to allow successful sampling also with the slimmest channel bronchoscopes. Although more alveolar tissue might be obtained when the TBB is performed with a large as compared to the small biopsy forceps, the difference in the size of the biopsy specimen does not always translate into higher overall diagnostic yield or complications [44, 45]. It might be difficult to open the cusps of larger biopsy forceps in the small peripheral airways, thus reducing the likelihood of obtaining desired alveolar specimen of lung parenchyma [46].

TBB specimens can be obtained blindly, with fluoroscopic guidance or with ultrasound or other navigational guidance. Many pediatric centers perform the TBB under fluoroscopic guidance. Biplane fluoroscopy equipment is necessary for accurate localization of the lesion, and the use of fluoroscopy during TBB especially improves the diagnostic yield of the procedure for focal lung infiltrates and lung masses [8]. TBB with fluoroscopy has not been associated with a significantly lower incidence of pneumothorax than biopsy performed without fluoroscopy [47].

Biopsy Technique

Adequate sedation and control of cough are essential for optimal biopsy procedure and to reduce the risk of pneumothorax. A complete endobronchial inspection of all segments of both lungs should be performed before the TBB because bleeding after lung biopsy might make it difficult to evaluate the airways. The choice of

biopsy site for focal lung diseases depends on radiological and fluoroscopic findings. In diffuse lung diseases, it is recommended to perform the biopsy from the dependent parts of the lungs in order to prevent any possible spilling into the other lobes in an event of bleeding.

After choosing the biopsy site, the distal tip of the bronchoscope is placed near or in the airway leading to the lesion or area of interest. In the absence of a localized radiological abnormality, biopsy of the lowers lobes may have a higher chance of a good yield for acute cellular rejection [48, 49]. Biopsy forceps are then advanced through the working channel of the bronchoscope until the tip is seen emerging for the distal end of the bronchoscope. If the blind technique is being performed, the forceps are advanced slowly into the airway until resistance is encountered (resistance signifies that the tip of the forceps has probably reached the pleura), the forceps are then pulled back approximately 1–2 cm, and if the patient is awake, the patient is instructed to take a deep breath and hold breath at maximum inspiration. This maneuver dilates the peripheral airway allowing cusps of the forceps open wide. Then the assistant is instructed to open the biopsy forceps and to advance gently until resistance is met, which is due to the fact that the open cusps are anchored at the bifurcation of the respiratory or the terminal bronchioles. If the patient experiences pain at this point, the forceps is withdrawn; the only pain-sensitive structure in the area is the visceral pleura. If no pain, the biopsy cusps are closed, and the forceps is gently retracted, taking a 2–4 mm parenchymal tissue sample with them. The assistant might feel a slight "pull"; although this feeling and actual movement of the lung infiltrate on fluoroscopy screen are useful markers for a good biopsy specimen, they are not always correct. There is no need to make forceful movements while withdrawing the biopsy forceps [8, 50].

The forceps and the biopsy specimen are pulled out through the working channel of the bronchoscope, and the tissue sample is inspected, removed from the forceps tip, and collected in saline for microbiologic analysis or a fixative, such as formalin, for histologic analysis. A sterile needle or a toothpick may be used to retrieve the specimen from the biopsy forceps. Before reinserting the forceps through the scope, it is important to make sure that the forceps is properly rinsed in sterile normal saline or exchanged. The biopsied area should be inspected for bleeding while the assistant is preparing the sample. Additional biopsies are usually taken while maintaining the wedged position as much as possible provided bleeding is minimal and if more than one biopsy is needed (e.g., sarcoidosis) or the biopsy attempt was unsuccessful [8, 21].

TBB with fluoroscopic guidance is similar to blind-TBB. The forceps are advanced into the distal airways under fluoroscopic guidance, and, prior to attempting the biopsy, the location of the forceps is confirmed fluoroscopically to verify that it is in the target area and not against the pleura (to minimize the risk of pneumothorax). Some fluoroscopes are planar and can only determine how lateral the forceps are, while others can rotate in different planes to provide more accurate three-dimensional information regarding the location of the forceps tip [50]. Radial probe ultrasound, computed tomography, and positron emission tomography or navigational tools could also be used to confirm placement of the forceps in a peripheral lung nodule or mass to increase diagnostic yield [8].

The number of biopsy specimens required for optimal diagnostic yield has been reported to be four to ten [51]. At least five pieces of well-expanded alveolated lung parenchyma are required for an assessment of acute rejection in lung transplantation cases. The bronchoscopist may need to submit more than five biopsies to provide this minimum number of adequately alveolated pieces, and possibly further biopsies if small bronchioles are required to be present [12].

Fluoroscopic examination is recommended at the conclusion of the procedure to rule out pneumothorax. A routine chest radiograph has a low diagnostic yield for pneumothorax after uncomplicated TBB procedure in clinically stable patients, but if there is any discomfort, such as shortness of breath or chest pain, chest radiogra-

phy should be performed to evaluate for possible pneumothorax [52]. After the procedure, it is important to monitor the patient for at least 2 h. Administration of anticoagulants and antiplatelet agents can be resumed 12–24 h after the procedure [21].

Specimen Handling

The quality and adequacy of transbronchial biopsies are difficult to assess during the procedure. There is controversy about how many alveoli should be considered adequate in the TBB samples. In some cases, the obtained tissue is suboptimal because of the small size and/or presence of crush artifacts. Transbronchial biopsies, even when performed by experienced physicians, obtain nondiagnostic bronchial tissue, cartilage, or clot in more than half of the biopsy attempts, and these tissue samples could be interpreted as high quality by physicians. Previous studies have proposed that alveolated tissue is more likely to float than nonalveolated tissue and that floating could be used as a sign predictive of high diagnostic yield. However, the "float sign," when applied to a heterogeneous group of TBB specimens, lacked both sensitivity and specificity in predicting diagnostic yield [1].

The biopsy samples are preserved in a container with 10% formalin for routine pathological examination. When infectious disease is likely, one or more tissue specimen may be submitted to the microbiology laboratory in sterile saline solution or sterile Ringer's lactate. Biopsy specimens for special studies such as electron microscopy, immunostaining, and flow cytometry should be collected and transported in consultation with the receiving pathology laboratory [8].

Limitations

Tranbronchial biopsies might miss the correct diagnosis when the disease is patchy or when visualization of whole pulmonary acini is needed to fully evaluate disease distribution. Examples include granulomatosis with polyangiitis (Wegener's granulomatosis) and other vasculitides that typically require examination of arteries and arterioles that are larger than those obtained by TBB and the idiopathic interstitial pneumonias, particularly idiopathic pulmonary fibrosis [50]. In patients with solitary lung nodules, traditional flexible bronchoscopy with TBB has a low diagnostic yield, and ancillary techniques are needed for better evaluation.

Complications

TBB is a safe, minimally invasive procedure with an estimated mortality of less than 0.05% [50, 53–55]. Optimal sedation, adequate topical anesthesia, and proper technique all reduce the incidence of complications related to the procedure. The major complications of TBB are pneumothorax and bleeding. Pneumothorax is estimated to occur in 0.7–2%, although rates up to 10% have been reported; less than half require tube thoracostomy drainage [53–58]. Patients receiving positive pressure ventilation are more likely to develop pneumothorax after transbronchial biopsies. TBB should not be performed bilaterally during the same bronchoscopic procedure on the same date due to delayed risk of bilateral pneumothorax. Appropriate fluoroscopic guidance during transbronchial biopsies reduces the risk of pneumothorax.

Bleeding is reported in 1–4% [50, 53]. With minor bleeding, watchful waiting with the bronchoscope is usually successful, and suctioning close to the area of the biopsy should be avoided. One of the techniques commonly used to control major procedural bleeding is the wedge technique, first described by Zavala in 1976 [21, 59]. In this technique, the bronchoscope is wedged into the appropriate segmental bronchus, and after maintaining bronchoscope in wedged position for about 5 min, the bronchoscope is gently withdrawn. Other options that are used by different centers for controlling bleeding include administration of iced saline, instillation of diluted epinephrine, positioning the patient with

the bleeding lung down, and, finally, placement of an endobronchial blocker. The neodymium-doped yttrium aluminum garnet (Nd:YAG) laser and argon plasma coagulation could also be useful for stopping bleeding [21].

Cryobiopsy

The use of cryoprobes to obtain alveolar TBB material during bronchoscopy is a newer technique. In this technique, a cryoprobe is inserted into the lung, cooled below freezing, and then retrieved with the lung tissue that has frozen onto it. This tissue is thawed in saline and then transferred to formalin and processed routinely for histologic evaluation. Artifacts associated with cryobiopsy are minimal [60]. Although the size of the specimen is usually much larger than that obtained with a biopsy forceps, they are still significantly smaller than surgical lung biopsies, and the risk of bleeding is reported to be higher than conventional TBB [41, 50, 57, 61, 62].

Conclusion and Future Directions

TBB is a safe and important tool in the evaluation of certain pediatric lung diseases, especially lung transplantation. Severe complications such as hemorrhage and pneumothorax are rare and can typically be managed conservatively. The performance of bronchoscopy should be considered based on clinical indications, rather than on the age or size of the patient, when a tissue diagnosis is needed. Its diagnostic success is higher in non-localized lesions and non-fibrotic diseases. Several recent techniques such as radial probe endobronchial ultrasound with guide sheath, electromagnetic navigation bronchoscopy, and virtual bronchoscopy navigation have been used to improve the diagnostic yield of TBB. The scarcity of published studies in this field in general underlines the need for further research, but meaningful advancement in the field will require multicenter collaboration.

References

1. Curley FJ, Johal JS, Burke ME, Fraire AE. Transbronchial lung biopsy: can specimen quality be predicted at the time of biopsy? Chest. 1998;113:1037–41.
2. Andersen HA, Fontana RS, Harrison EG Jr. Transbronchoscopic lung biopsy in diffuse pulmonary disease. Dis Chest. 1965;48:187–92.
3. Andersen HA, Fontana RS. Transbronchoscopic lung biopsy for diffuse pulmonary diseases: technique and results in 450 cases. Chest. 1972;62:125–8.
4. Clark RA, Gray PB, Townshend RH, Howard P. Transbronchial lung biopsy: a review of 85 cases. Thorax. 1977;32:546–9.
5. Levin DC, Wicks AB, Ellis JH Jr. Transbronchial lung biopsy via the fiberoptic bronchoscope. Am Rev Respir Dis. 1974;110:4–12.
6. Mullins D, Livne M, Mallory GB Jr, Kemp JS. A new technique for transbronchial biopsy in infants and small children. Pediatr Pulmonol. 1995;20:253–7.
7. Visner GA, Faro A, Zander DS. Role of transbronchial biopsies in pediatric lung diseases. Chest. 2004;126:273–80.
8. Jain P, Hadique S, Mehta AC. Transbronchial lung biopsy. In: Mehta A, Jain P, editors. Interventional bronchoscopy: a clinical guide. Totowa: Humana Press; 2013. p. 15–44.
9. Valentine VG, et al. Single-institution study evaluating the utility of surveillance bronchoscopy after lung transplantation. J Heart Lung Transplant. 2009;28:14–20.
10. Hayes D, et al. Surveillance transbronchial biopsies in infant lung and heart – lung transplant recipients. Pediatr Transplant. 2013;17:670–5.
11. Roden AC, et al. Diagnosis of acute cellular rejection and antibody-mediated rejection on lung transplant biopsies: a perspective from members of the pulmonary pathology society. Arch Pathol Lab Med. 2017;141:437–44.
12. Stewart S, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant. 2007;26:1229–42.
13. Bhorade SM, et al. Interobserver variability in grading transbronchial lung biopsy specimens after lung transplantation. Chest. 2013;143:1717–24.
14. Eber E, et al. ERS statement: interventional bronchoscopy in children. Eur Respir J. 2017;50:1700901.
15. Elizur A, et al. Lung transplantation in infants and toddlers from 1990 to 2004 at St. Louis Children's Hospital. Am J Transplant. 2009;9:719–26.
16. Trulock EP, et al. The role of transbronchial lung biopsy in the treatment of lung transplant recipients. An analysis of 200 consecutive procedures. Chest. 1992;102:1049–54.
17. Hopkins PM, et al. Prospective analysis of 1,235 transbronchial lung biopsies in lung transplant recipients. J Heart Lung Transplant. 2002;21:1062–7.

18. McWilliams TJ, Williams TJ, Whitford HM, Snell GI. Surveillance bronchoscopy in lung transplant recipients: risk versus benefit. J Heart Lung Transplant. 2008;27:1203–9.
19. Stover DE, et al. Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. Ann Intern Med. 1984;101:1–7.
20. Bae KM, et al. The relevance of biopsy in tuberculosis patients without human immunodeficiency virus infection. Am J Trop Med Hyg. 2015;92:636–40.
21. Lessnau K. Transbronchial biopsy. Medscape. http://www.emedicine.medscape.com. Accessed on 30 May 2018.
22. Wallace JM, Catanzaro A, Moser KM, Harrell JH 2nd. Flexible fiberoptic bronchoscopy for diagnosing pulmonary coccidioidomycosis. Am Rev Respir Dis. 1981;123:286–90.
23. Salzman SH, Smith RL, Aranda CP. Histoplasmosis in patients at risk for the acquired immunodeficiency syndrome in a nonendemic setting. Chest. 1988;93:916–21.
24. Sevim T, et al. Transbronchial biopsy: our experience in 5 year. Eurasian J Pulmonol. 2017;19:41–5.
25. Casoni G, Gurioli C, Poletti V. Transbronchial pulmonary biopsies. Monaldi Arch Chest Dis. 2015;75:39–41.
26. Wallace JM, Deutsch AL, Harrell JH, Moser KM. Bronchoscopy and transbronchial biopsy in evaluation of patients with suspected active tuberculosis. Am J Med. 1981;70:1189–94.
27. Danek SJ, Bower JS. Diagnosis of pulmonary tuberculosis by flexible fiberoptic bronchoscopy. Am Rev Respir Dis. 1979;119:677–9.
28. Charoenratanakul S, Dejsomritrutai W, Chaiprasert A. Diagnostic role of fiberoptic bronchoscopy in suspected smear negative pulmonary tuberculosis. Respir Med. 1995;89:621–3.
29. Tamura A, et al. The value of fiberoptic bronchoscopy in culture-positive pulmonary tuberculosis patients whose pre-bronchoscopic sputum specimens were negative both for smear and PCR analyses. Intern Med. 2010;49:95–102.
30. Kennedy DJ, Lewis WP, Barnes PF. Yield of bronchoscopy for the diagnosis of tuberculosis in patients with human immunodeficiency virus infection. Chest. 1992;102:1040–4.
31. Chan C, et al. Bronchoscopy and tuberculostearic acid assay in the diagnosis of sputum smear-negative pulmonary tuberculosis: a prospective study with the addition of transbronchial biopsy. QJM. 1992;82:15–23.
32. Griffith DE, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367–416.
33. Oliveira CC, et al. Evaluation of the use of transbronchial biopsy in patients with clinical suspicion of interstitial lung disease. J Bras Pneumol. 2011;37:168–75.
34. Bensard DD, McIntyre RC Jr, Waring BJ, Simon JS. Comparison of video thoracoscopic lung biopsy to open lung biopsy in the diagnosis of interstitial lung disease. Chest. 1993;103:765–70.
35. Gilman MJ, Wang KP. Transbronchial lung biopsy in sarcoidosis. An approach to determine the optimal number of biopsies. Am Rev Respir Dis. 1980;122:721–4.
36. Bilaçeroğlu S, Perim K, Günel O, Cağirici U, Büyükşirin M. Combining transbronchial aspiration with endobronchial and transbronchial biopsy in sarcoidosis. Monaldi Arch Chest Dis. 1999;54:217–23.
37. Prakash UBS. Endobronchial biopsy for sarcoidosis. A prospective study. J Bronchology Interv Pulmonol. 2001;8:321.
38. Lacasse Y, Fraser RS, Fournier M, Cormier Y. Diagnostic accuracy of transbronchial biopsy in acute farmer's lung disease. Chest. 1997;112:1459–65.
39. Gruden JF, Webb WR, Naidich DP, McGuinness G. Multinodular disease: anatomic localization at thin-section CT – multireader evaluation of a simple algorithm. Radiology. 1999;210:711–20.
40. Wall CP, Gaensler EA, Carrington CB, Hayes JA. Comparison of transbronchial and open biopsies in chronic infiltrative lung diseases. Am Rev Respir Dis. 1981;123:280–5.
41. Shim HS, Park MS, Park IK. Histopathologic findings of transbronchial biopsy in usual interstitial pneumonia. Pathol Int. 2010;60:373–7.
42. Mazzone P, Jain P, Arroliga AC, Matthay RA. Bronchoscopy and needle biopsy techniques for diagnosis and staging of lung cancer. Clin Chest Med. 2002;23:137–58, ix.
43. Rivera MP, Mehta AC, American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132:131S–48S.
44. Loube DI, et al. The effect of forceps size on the adequacy of specimens obtained by transbronchial biopsy. Am Rev Respir Dis. 1993;148:1411–3.
45. Wang KP, et al. Comparison of standard and large forceps for transbronchial lung biopsy in the diagnosis of lung infiltrates. Endoscopy. 1980;12:151–4.
46. Smith LS, Seaquist M, Schillaci RF. Comparison of forceps used for transbronchial lung biopsy. Bigger may not be better. Chest. 1985;87:574–6.
47. Smyth CM, Stead RJ. Survey of flexible fibreoptic bronchoscopy in the United Kingdom. Eur Respir J. 2002;19:458–63.
48. Wong JY, Westall GP, Snell GI. Bronchoscopic procedures and lung biopsies in pediatric lung transplant recipients. Pediatr Pulmonol. 2015;50:1406–19.
49. Hasegawa T, Iacono AT, Yousem SA. The anatomic distribution of acute cellular rejection in the allograft lung. Ann Thorac Surg. 2000;69:1529–31.
50. King TE, Raj R. Role of lung biopsy in the diagnosis of interstitial lung biopsy. Post TW, editor. UpToDate. Waltham: UpToDate Inc. http://www.uptodate.com. Accessed on 30 May 2018.
51. Roethe RA, Fuller PB, Byrd RB, Hafermann DR. Transbronchoscopic lung biopsy in sarcoidosis.

Optimal number and sites for diagnosis. Chest. 1980;77:400–2.
52. Frazier WD, Pope TL Jr, Findley LJ. Pneumothorax following transbronchial biopsy. Low diagnostic yield with routine chest roentgenograms. Chest. 1990;97:539–40.
53. Bradley B, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008;63(Suppl 5):v1–58.
54. Sehgal IS, et al. A prospective randomized controlled trial comparing the efficacy and safety of cup vs Alligator forceps for performing Transbronchial lung biopsy in patients with sarcoidosis. Chest. 2016;149:1584–6.
55. Sindhwani G, Shirazi N, Sodhi R, Raghuvanshi S, Rawat J. Transbronchial lung biopsy in patients with diffuse parenchymal lung disease without "idiopathic pulmonary fibrosis pattern" on HRCT scan – experience from a tertiary care center of North India. Lung India. 2015;32:453–6.
56. Poletti V, Chilosi M, Olivieri D. Diagnostic invasive procedures in diffuse infiltrative lung diseases. Respiration. 2004;71:107–19.
57. Tomassetti S, et al. Transbronchial biopsy is useful in predicting UIP pattern. Respir Res. 2012;13:96.
58. Descombes E, Gardiol D, Leuenberger P. Transbronchial lung biopsy: an analysis of 530 cases with reference to the number of samples. Monaldi Arch Chest Dis. 1997;52:324–9.
59. Zavala DC. Pulmonary hemorrhage in fiberoptic transbronchial biopsy. Chest. 1976;70:584–8.
60. Colby TV, Tomassetti S, Cavazza A, Dubini A, Poletti V. Transbronchial cryobiopsy in diffuse lung disease: update for the pathologist. Arch Pathol Lab Med. 2017;141:891–900.
61. Berbescu EA, Katzenstein A-LA, Snow JL, Zisman DA. Transbronchial biopsy in usual interstitial pneumonia. Chest. 2006;129:1126–31.
62. Raghu G, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.

Endobronchial Ultrasound

35

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Introduction

Since its initial introduction into the bronchoscopic diagnostic repertoire in the early 1990s, EBUS has revolutionized adult bronchoscopy with its ability to localize lesions, obtain diagnostic tissue, and avoid unnecessary surgical interventions [2–4]. Advances in engineering enabled the reduction of ultrasound size to be compatible with bronchoscopy, and the integration of a fluid-filled balloon allowed for sound wave transmission in the central tracheobronchial tree where ultrasonographic coupling to the airway is very limited. At present there are two distinct types of EBUS technology available: (*1*) radial probe EBUS (r-EBUS)—of which there are two subtypes: (*a*) ultra-miniature radial probe EBUS (UM-EBUS) and (*b*) radial balloon probe EBUS (RB-EBUS)—and (*2*) convex probe or curvilinear EBUS (CP-EBUS). In general, UM-EBUS allows for localization of peripheral lung lesions but currently does not allow for real-time lesion visualization during biopsy; RB-EBUS assists with proximal airway structural assessment; and CP-EBUS enables real-time ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes and/or central masses or nodules. This chapter will (*i*) review the current usages of each type of EBUS in adults, (*ii*) discuss EBUS utilization in the pediatric population, and (*iii*) explore the future possibilities of pediatric application of EBUS modalities.

Ultra-Miniature Radial Probe EBUS

The evaluation of peripheral pulmonary nodules remains a challenging diagnostic dilemma for chest physicians. In adults and children alike, multiple procedures exist to acquire a biopsy for tissue diagnosis. A surgical biopsy provides a larger tissue sample and a higher diagnostic yield but with increased morbidity and cost. Computed tomography (CT)–guided transthoracic needle aspiration (TTNA) has a diagnostic yield of 70–90% but comes with a 10–40% risk of pneumothorax [5–7]. Even prior to the more widespread use of r-EBUS, fiberoptic bronchoscopy modalities such as brushing, lavage, and transbronchial biopsy were known to have a lower complication rate but a lower sensitivity for the diagnosis of peripheral pulmonary nodules (10–60%) [8, 9]. The r-EBUS probe was the first EBUS technology to be developed, and in 1990,

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_35

Hürter and Hanrath first described its use in identifying peribronchial tumors and blood vessels in addition to assistance with endobronchial stent placement [10, 11]. In 2002, Herth et al. demonstrated that r-EBUS could be used to guide transbronchial lung biopsies of specific pulmonary lesions [12]. Multiple subsequent studies in adults have suggested that the bronchoscopic diagnostic yield for peripheral pulmonary nodules has improved to 30–80% with UM-EBUS probe usage to localize peripheral pulmonary lesions. The diagnostic yield variation depends on many factors including lesion size, location, concentric versus eccentric UM-EBUS view, and use of adjunctive technologies such as fluoroscopy, guide sheath kits, virtual navigational bronchoscopy, electromagnetic navigation, and peripheral transbronchial needle aspiration [13–21]. More recent meta-analyses have demonstrated that the overall diagnostic yield of UM-EBUS is likely closer to 50–70% overall and may be closer to 70% for diagnosing malignancy and 40–60% for benign lesions [22–25]. Overall, it has become clear that the diagnostic yield for the evaluation of peripheral pulmonary nodules is improved with UM-EBUS guidance compared to traditional fiberoptic bronchoscopy alone with a complication rate significantly lower than that of CT-guided TTNA (<3% vs >10%) [7, 23, 24].

The currently available UM-EBUS probes incorporate a 20 MHz ultrasound transducer that uses a mechanical radial scanning method to provide a circumferential view via direct contact with distal airways and displays images in B mode perpendicular to the longitudinal axis of the probe (Fig. 35.1a). The probes vary in maximum distal diameter from 1.4 mm to 1.70 mm and are compatible with various guide sheath kits. The smaller probes have slightly more flexibility to reach challenging locations in the api-

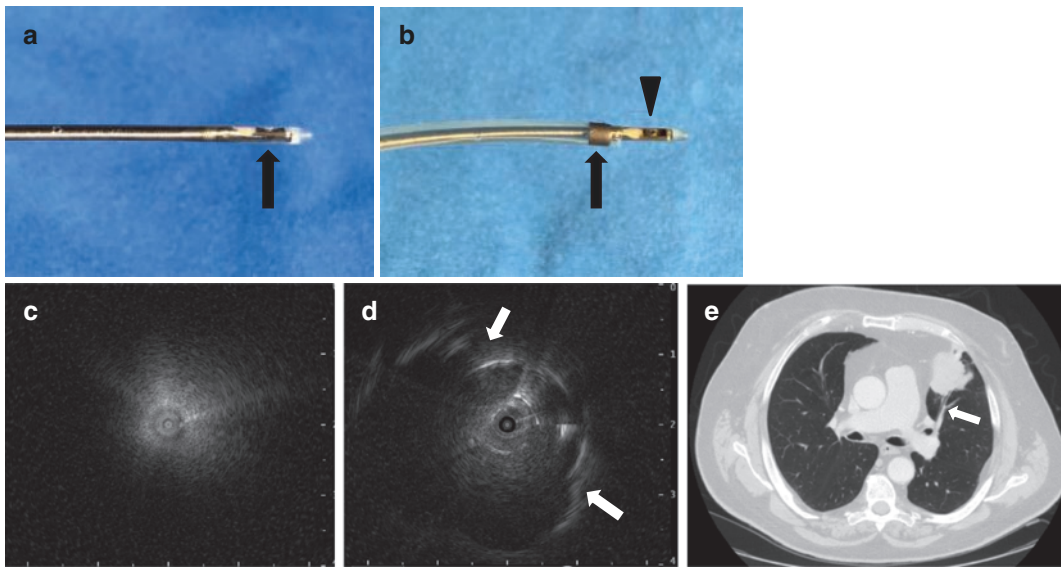

Fig. 35.1 (**a**) Image of UM-EBUS probe with the arrow marking the circulating piezoelectrode at the distal tip of the probe that gives a 360 degree view of the surrounding lung parenchyma. (**b**) The UM-EBUS probe is inserted into the guide sheath to allow for an extended working channel to pass biopsy instruments once the lesion is found with UM-EBUS. The arrowhead marks the peizoelectrode extending just beyond the distal end of the guide sheath, while the arrow marks the radio-opaque marker at the distal end of guide sheath that allows the fluoroscopic visualization of the distal tip of the guide sheath as biopsy instruments are passed. (**c**) Snowstorm appearance of normal aerated lung tissue. The circle in the middle of the image is the UM-EBUS probe in the airway generating a 360 degree view of the surrounding lung parenchyma. (**d**) Left upper lobe mass identified as a concentric isoechoic image on UM-EBUS. The arrows denote where the lesion ends and aerated lung begins which generates a hyperechoic border. (**e**) The corresponding lesion and airway leading to the lesion (arrow) through which the UM-EBUS probe was passed can be seen on CT chest imaging

cal and posterior lung segments. Guide sheaths function as an extended working channel once a lesion is found with UM-EBUS and remain at the lesion airway position so biopsy instruments can be passed expeditiously through the guide sheath without losing lesion location (Fig. 35.1b). In the pediatric population, there may be an advantage to using the smaller probes as a narrower bronchoscope with a smaller working channel can be utilized, thereby allowing for use in younger patients with less procedural ventilatory interference.

To perform real-time evaluation of a peripheral parenchymal lesion, the UM-EBUS probe is connected to a mechanical drive unit, and the bronchoscopist inserts the probe through the working channel of a compatible flexible bronchoscope with or without a guide sheath. Using corresponding CT chest imaging and/or navigational technology for spatial guidance, the bronchoscopist advances the UM-EBUS probe into sequential bronchial sub-segments until the normal lung "snowstorm" appearance (Fig. 35.1c) is replaced by an isoechoic signal consistent with lesion localization (Fig. 35.1d). The snowstorm effect is created by the reverberation of the ultrasound waves off the normal alveolated lung parenchyma while a lesion is solid tissue and generates an isoechoic signal characteristic of solid tissue. This lesion position can then be marked by a guide sheath, and/or fluoroscopy. The UM-EBUS probe is removed to allow for guided biopsies of the parenchymal lesion using brushes, forceps, and/or needle biopsy through the guide sheath. Currently, the bronchoscopist cannot visualize the lesion real time with UM-EBUS while utilizing the various biopsy modalities [2].

Technical limitations related to pediatric airway diameter and bronchoscope working channel size to accommodate the UM-EBUS probe have limited UM-EBUS pediatric utilization. Due to the UM-EBUS physical size, its utilization in the pediatric population is limited to children with an airway diameter that can accommodate a bronchoscope with a 2.0 mm working channel and allow for adequate ventilation via an artificial airway. A 5.5–6.0 mm endotracheal tube and a size 2.5 laryngeal mask airway are options to accommodate a bronchoscope with a 2.0 mm working channel [26, 27]. In addition, the amount of radiation exposure to a pediatric patient during UM-EBUS must be considered as fluoroscopy is used concomitantly to confirm lesion localization and perform biopsies [28]. It has been suggested that the mean fluoroscopy time for a UM-EBUS procedure is ~96 seconds, and the mean effective radiation dose to patients is ~0.49 milliSieverts which is approximately equivalent to 10 chest X-rays [29]. A recent report in immunocompromised children demonstrated that UM-EBUS was able to identify lesions in 84% of procedures and detected clinically significant microbial pathogens in 62% of cases (Bouso et al, AJRCCM 201:384-386. Given the small samples size in this report (19 patients), further studies are necessary to determine if UM-EBUS for the evaluation of peripheral lung lesions in children is feasible and safe and improves the bronchoscopic diagnostic yield.

Radial Balloon Probe EBUS

As UM-EBUS requires direct probe contact with the airway for ultrasonographic coupling, visualization of lesions juxtaposed to the larger central airways is difficult given the poor circumferential apposition of the UM-EBUS probe to the larger airway endobronchial surfaces. Thus, a r-EBUS probe was developed that incorporates a saline-filled balloon at its distal tip to provide a sound wave–transducing medium from the r-EBUS probe to the airway wall (RB-EBUS, Fig. 35.2). The RB-EBUS probe currently available (UM-BS20-26R-3; Olympus; Tokyo, Japan) has a 20 MHz ultrasound transducer that uses a mechanical radial scanning method to provide a 360° circumferential view via balloon contact with proximal airways and displays images in B mode perpendicular to the longitudinal axis of the probe. It has a 2.6 mm maximum diameter, a 205 cm working length, and requires a ≥2.8 mm bronchoscope working channel.

In the adult population, the RB-EBUS can provide ≤1 mm resolution of the paratracheal and peribronchial structures allowing the description

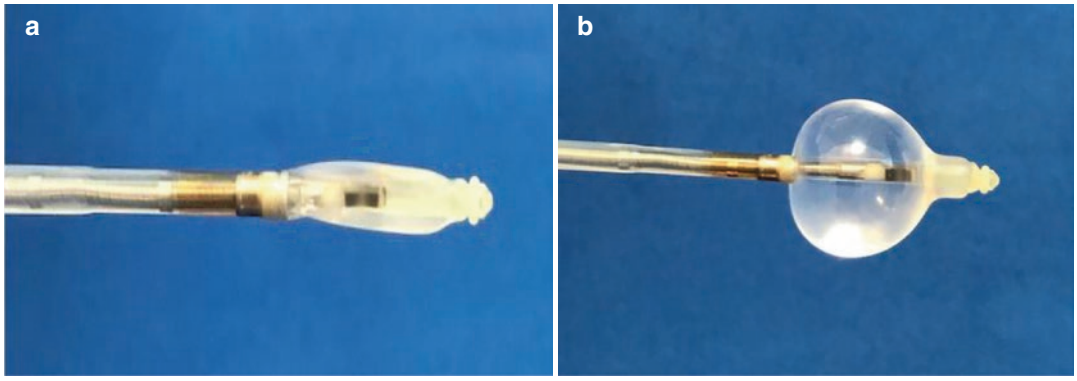

Fig. 35.2 RB-EBUS with uninflated (**a**) and saline-filled balloon (**b**). The peizoelectrode is in the center of the saline-filled balloon and gives a 360 degree view of the surrounding structures of the central tracheobronchial tree

of five to seven distinct layers of the central airway walls [30]. With this resolution, RB-EBUS can accurately (92–95% sensitivity) assess tumor invasion into the proximal airway walls [30–32]. In fact, RB-EBUS has been demonstrated to be superior to CT scans in differentiating central thoracic malignancy proximal airway involvement which may impact therapeutic management decisions (Fig. 35.3) [33]. Moreover, RB-EBUS has also been demonstrated to be useful in distinguishing different clinical phenotypes in relapsing polychondritis and asthma [34–36]. These adult RB-EBUS applications imply that there may be a role for RB-EBUS in select circumstances in the pediatric population; however, its utilization may be limited to older children by the need for a large bronchoscope with a 2.8 mm working channel. There are no reported usages of the RB-EBUS probe in the pediatric literature, likely because of the emergence and dramatic clinical impact of the CP-EBUS bronchoscope in the adult population.

Convex Probe EBUS-TBNA

In 1978, Wang et al. first demonstrated that transbronchial needle aspiration (TBNA) was feasible via flexible bronchoscopy and capable of providing a tissue diagnosis for paratracheal tumors [37]. Thereafter, endobronchial landmarks were used to guide TBNA via bronchoscopy, and the procedure was demonstrated to be useful for the evaluation of mediastinal and hilar abnormalities; however, the diagnostic yield of this conventional TBNA (c-TBNA) varied greatly ranging from 40–90% even when performed by experienced operators [38–42]. In 2004, Yasufuku et al. first demonstrated that a newly developed integrated CP-EBUS bronchoscope was capable of safely and accurately providing real-time EBUS guidance for TBNA (CP EBUS-TBNA) [43]. In adults, CP EBUS-TBNA has largely become the initial diagnostic gold standard procedure for minimally-invasive evaluation of paratracheal, central mediastinal, and hilar pulmonary abnormalities, boasting a sensitivity, specificity, and accuracy in the high 90% range. CP-EBUS diagnostic utility has been shown for both malignant and non-malignant conditions [43–52]. In fact, for lung cancer staging, the diagnostic yield of CP EBUS-TBNA has been demonstrated to be superior to the previous gold standard of cervical mediastinoscopy [46–47, 50, 53–54]. Moreover, it has become the initial diagnostic procedure for mediastinal and hilar lymphadenopathy suspicious for sarcoidosis, tuberculosis, or lymphoma [51, 55–62]. Importantly, the procedure itself has been demonstrated to be safe with only a limited number of serious complications being reported [63, 64].

There are currently several CP-EBUS bronchoscopes available each of which incorporates a 5–12 MHz curvilinear ultrasound transducer into the distal tip of the bronchoscope that scans at 90° from the bronchoscope longitudinal axis (Fig. 35.4). While these available scopes vary slightly in their ultrasound field of view and

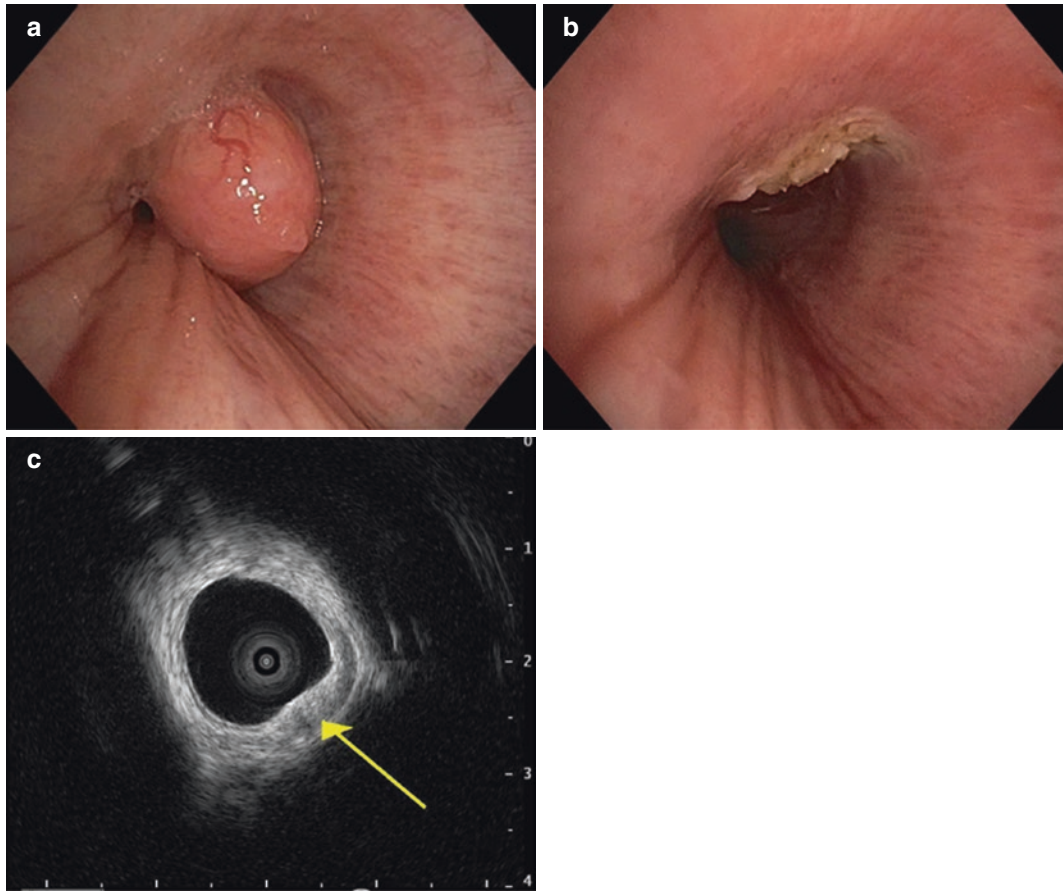

Fig. 35.3 (**a**) Endobronchial lesion present in the distal left mainstem bronchus. (**b**) The lesion was removed with an electrocautery snare. (**c**) To assess the lesion penetration depth into the airway wall, the RB-EBUS probe was placed onto the base of the lesion. The ultrasound image demonstrates that the lesion does not pass through the depth of the airway wall

video direction of view, the CP-EBUS revolution is real-time aspiration visualization of the lymph node or lesion. To perform CP EBUS-TBNA, the bronchoscopist scans the paratracheal or perihilar space to identify the lesion of interest and then inserts a flexible biopsy needle (19-, 21-,-22-, or 25-gauge) through the CP-EBUS working channel to pierce through the tracheobronchial wall into the lymph node or lesion of interest under real-time EBUS imaging guidance. To improve CP-EBUS image quality from poor ultrasonographic coupling to the airway wall, a saline-filled balloon surrounding the transducer can be inflated (Fig. 35.4b). Furthermore, color Doppler ultrasound can help confirm vascular structures to minimize unintended vascular puncture and to assess intralesional vascular characteristics. To avoid specimen contamination with bronchial epithelium or tracheobronchial cartilage, a removable stylet is used during the initial needle insertion through the airway wall. Once through the airway wall, the stylet is removed and repeated needle agitations through the lesion or lymph node to obtain a tissue sample are performed (Fig. 35.5). The application of suction to the needle can be performed although studies have demonstrated that this suction may not affect diagnostic yield [62, 65].

Regarding the type of anesthesia used for the procedure, there is no clear consensus recommendation, and both conscious sedation and general anesthesia are reasonable options to assist

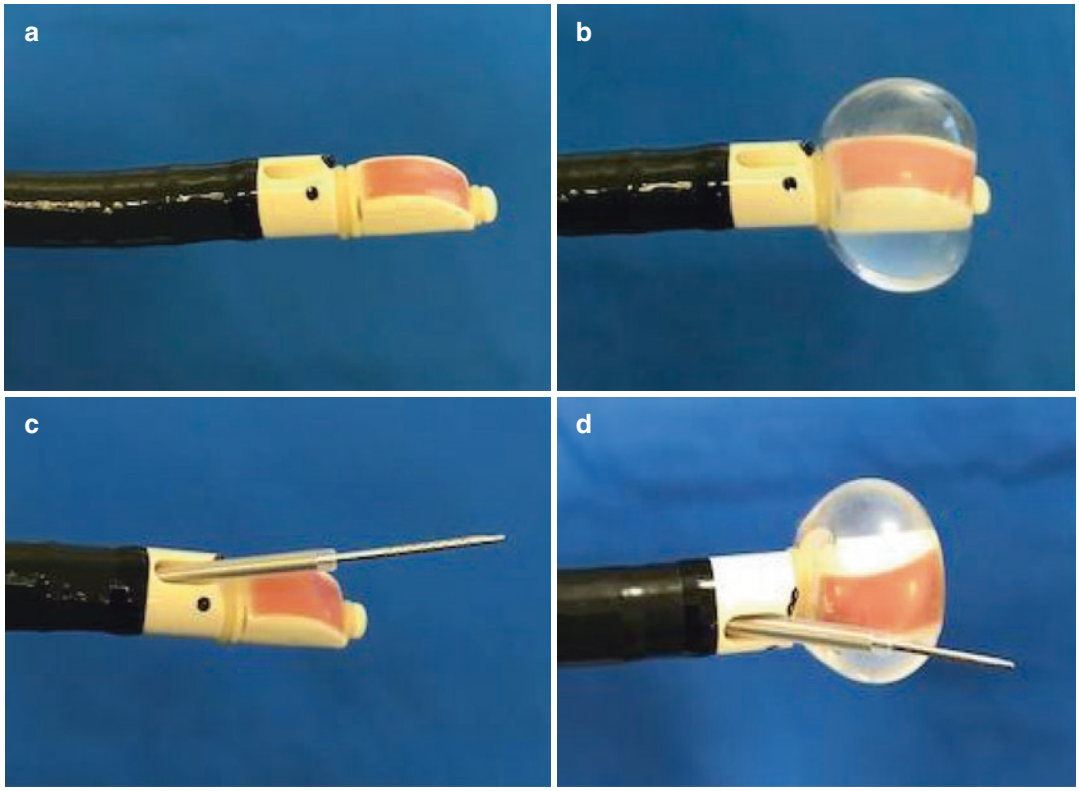

Fig. 35.4 Distal tip of the CP EBUS bronchoscope (**a**) with saline-filled balloon (**b**), 22-gauge needle with sheath extended (**c**), and saline-filled balloon and 22-gauge needle with sheath extended (**d**)

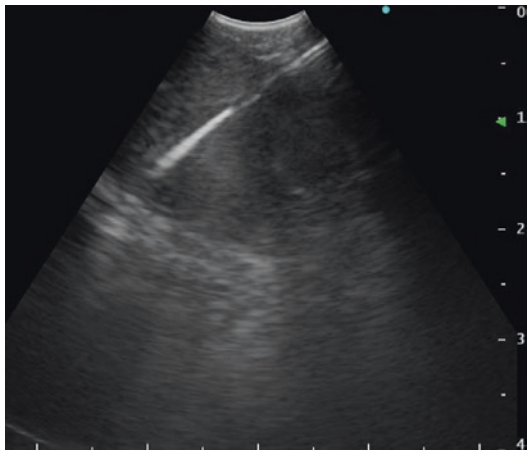

Fig. 35.5 CP EBUS-TBNA of a right paratracheal mediastinal lymph node with 22-gauge needle. The needle is the hyperechoic line in the isoechoic lymph node entering from the top left of the EBUS image

with CP EBUS-TBNA patient tolerance [62, 66–68]. Using either a natural orifice (mouth or nose) or an artificial airway (laryngeal mask airway or an endotracheal tube) for bronchoscopic airway access is safe and feasible, and the decision will largely depend on local expertise and institutional practice [62, 69]. This decision should be made in a multi-disciplinary fashion in conjunction with the anesthesiology team [70]. One factor to consider is the larger outer diameter of all CP-EBUS scopes compared to traditional bronchoscopies when making the procedural airway choice. Maintaining adequate ventilation when the CP-EBUS scope fills the majority of the lumen of a smaller airway device (LMA or ETT) can be challenging and must be considered. One option with smaller airways and ventilation limitations would be to insert the scope, advance

quickly to the targeted lesion, obtain a CP EBUS-TBNA biopsy, and remove the scope to allow ventilation to resume. Several minutes of post-biopsy ventilation should allow for the resumption of normal oxygenation and ventilation that may have been limited during scope insertion. A repeat biopsy can be performed once the team is reassured oxygenation and ventilation are stable.

Periihilar lesions in children usually involve ultrasound or CT-guided transthoracic fine needle aspiration [71]. If the initial procedure is non-diagnostic, subsequent recommended procedures include video-assisted thoracic surgery, mediastinoscopy, or thoracotomy [72–74]. As a result, CP-EBUS could provide a minimally-invasive option for these central lesions in the pediatric population. The application of CP EBUS-TBNA in children has not been well established for a variety of reasons, including the much lower incidence of malignancy and other central pulmonary lesions in this population and the smaller airway caliber making scope access while maintaining ventilation challenging, but there is an expanding pediatric population experience [1, 75–77].

The currently available pediatric literature on CP EBUS-TBNA is limited to case series, case reports, and retrospective studies [78–84]. The largest and most recent multi-center retrospective study by Dhooria et al. in 2016 demonstrated that of the 54 children (85% between the ages of 13–17 years) undergoing CP EBUS-TBNA, the diagnostic yield was 58.4% with no major complications reported [80]. A similar multi-center retrospective study by Gilbert et al. in 2014 included 21 pediatric patients (ages 1.5–18 years; mean age of 13.7 years) who underwent CP EBUS-TBNA for the evaluation of mediastinal or hilar abnormalities and demonstrated a diagnostic yield of 48% with no associated major complications [81]. The diagnoses obtained in both studies included malignancies, granulomatous diseases, and infectious diseases. The diagnostic rate may fall short of that demonstrated for adult central thoracic lesions given the lower incidence of malignancy relative to infection in the pediatric population compared to the adult population. Thus, using the currently available CP-EBUS bronchoscope, it is feasible and safe to consider CP EBUS-TBNA in select children with mediastinal and hilar lesions or lymphadenopathy. From a technical perspective and as discussed previously, it is important to consider a patient's airway diameter in relation to the larger CP-EBUS bronchoscope outer diameter (minimum size 6.7 mm) when evaluating a patient for CP EBUS-TBNA candidacy as transient intraprocedural airflow obstruction may occur [85, 86]. This is especially important in younger children with smaller airway caliber or pediatric patients with significant hypoxia. In patients whose risk of airflow obstruction is deemed to be prohibitively high, access to a central mediastinal lesion may be feasible by inserting the CP-EBUS bronchoscope into the esophagus for localization and lesion biopsy [87–91]. As suggested by several researchers [26, 81, 92], CP EBUS-TBNA use in children is likely to increase especially with the recent development of a new thin convex probe EBUS (TCP-EBUS) bronchoscope that has been tested in porcine and ex vivo human lungs at the time of this writing [93, 94]. This prototype EBUS bronchoscope (BF-Y0055; Olympus; Tokyo, Japan) has a thinner outer diameter of 5.9 mm which may allow access to smaller airways with less concern for ventilation limitations. This novel TCP-EBUS bronchoscope uses a dedicated 25-gauge needle for TBNA and can access nearly all segmental bronchi in ex vivo human lungs [94]. Pending further studies in human subjects and widespread availability of the TCP-EBUS bronchoscope, future application of this smaller bronchoscope in the pediatric population appears to be logical given the existing literature demonstrating the safety and efficacy of the current CP EBUS-TBNA in children.

Future Directions

Over the past 20 years following the advent of EBUS technologies, its utilization in the adult population has transitioned from interventional

pulmonary centers of excellence to virtually every adult pulmonary training program and many community practices. Similarly, as pediatric pulmonary physicians become more aware of and capable with EBUS utilization in the pediatric population, more pediatric patients may benefit from EBUS technologies rather than more invasive procedures. More investigation is needed to identify the value of UM-EBUS probe for peripheral lesion localization and biopsy. RB-EBUS may have unique applications in severe asthma, central airway malacia, or congenital airway stenoses to better understand the nature of the airway wall and what therapies may best be employed in these disease processes.

Conclusion

In summary, EBUS technology has become an invaluable tool available to the pulmonologist. In the adult patient population, r-EBUS is routinely used to localize and guide the biopsies of peripheral pulmonary lesions while CP EBUS-TBNA has created a paradigm shift in the minimally-invasive diagnosis of mediastinal and hilar abnormalities. While the application of EBUS in the pediatric population has been limited so far, initial studies have demonstrated that the current standard CP-EBUS bronchoscope can be used safely and effectively in children. The development of a new prototype thin CP-EBUS bronchoscope will likely further expand capacity to biopsy central mediastinal lesions in the pediatric population. Further experience with UM-EBUS is needed to demonstrate the utility and safety of UM-EBUS in the localization and biopsy of pediatric peripheral parenchymal lesions.

References

1. Neville H, Hogan A, Zhuge Y, et al. Incidence and outcomes of malignant pediatric lung neoplasms. J Surg Res. 2009;156(2):224–30. https://www.clinicalkey.es/playcontent/1-s2.0-S0022480409002005. https://doi.org/10.1016/j.jss.2009.03.100.
2. Vachani A, Sterman DH. Diagnostic bronchoscopy, transthoracic needle biopsy, and related procedures. In: Grippi MA, Elias JA, Fishman JA, et al., editors. Fishman's pulmonary diseases and disorders. 5th ed. New York: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1344&sectionid=81187775.
3. Haas AR, Vachani A, Sterman DH. Advances in diagnostic bronchoscopy. Am J Respir Crit Care Med. 2010;182(5):589–97. https://www.ncbi.nlm.nih.gov/pubmed/20378726. https://doi.org/10.1164/rccm.201002-0186CI.
4. Panchabhai TS, Mehta AC. Historical perspectives of bronchoscopy. Connecting the dots. Ann Am Thorac Soc. 2015;12(5):631–41.
5. Ohno Y, Hatabu H, Takenaka D, et al. CT-guided transthoracic needle aspiration biopsy of small (<= 20 mm) solitary pulmonary nodules. Am J Roentgenol. 2003;180(6):1665–9. http://www.ajronline.org/cgi/content/abstract/180/6/1665. https://doi.org/10.2214/ajr.180.6.1801665.
6. Yeow K, Su I, Pan K, et al. Risk factors of pneumothorax and bleeding: multivariate analysis of 660 CT-guided coaxial cutting needle lung biopsies. Chest. 2004;126(3):748. https://www.ncbi.nlm.nih.gov/pubmed/15364752
7. Wang W, Yu L, Wang Y, et al. Radial EBUS versus CT-guided needle biopsy for evaluation of solitary pulmonary nodules. Oncotarget. 2018;9(19):15122–31. https://www.ncbi.nlm.nih.gov/pubmed/29599932. https://doi.org/10.18632/oncotarget.23952.
8. Schreiber G, McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: summary of published evidence. Chest. 2003;123(1 Suppl):115S. https://www.ncbi.nlm.nih.gov/pubmed/12527571
9. Baaklini WA, Reinoso MA, Gorin AB, Sharafkaneh A, Manian P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Chest. 2000;117(4):1049–54. https://www.sciencedirect.com/science/article/pii/S001236921532804X. https://doi.org/10.1378/chest.117.4.1049.
10. Hürter T, Hanrath P. Endobronchial sonography in the diagnosis of pulmonary and mediastinal tumors. Deutsche medizinische Wochenschrift (1946). 1990;115(50):1899. https://www.ncbi.nlm.nih.gov/pubmed/2257778
11. Hürter T, Hanrath P. Endobronchial sonography: feasibility and preliminary results. Thorax. 1992;47(7):565–7. https://www.ncbi.nlm.nih.gov/pubmed/1412103. https://doi.org/10.1136/thx.47.7.565.
12. Herth FJF, Ernst A, Becker HD. Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. Eur Respir J. 2002;20(4):972–4. http://erj.ersjournals.com/cgi/content/abstract/20/4/972. https://doi.org/10.1183/09031936.02.00032001.
13. Paone G, Nicastri E, Lucantoni G, et al. Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. Chest. 2005;128(5):3551–7.

https://www.sciencedirect.com/science/article/pii/S0012369215529292. https://doi.org/10.1378/chest.128.5.3551.
14. Kurimoto N, Miyazawa T, Okimasa S, et al. Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest. 2004;126(3):959–65. https://www.sciencedirect.com/science/article/pii/S0012369215312423. https://doi.org/10.1378/chest.126.3.959.
15. Herth FJF, Eberhardt R, Becker HD, Ernst A. Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: a prospective trial. Chest. 2006;129(1):147. https://www.ncbi.nlm.nih.gov/pubmed/16424425
16. Yamada N, Yamazaki K, Kurimoto N, et al. Factors related to diagnostic yield of transbronchial biopsy using endobronchial ultrasonography with a guide sheath in small peripheral pulmonary lesions. Chest. 2007;132(2):603–8. https://www.sciencedirect.com/science/article/pii/S0012369215374572. https://doi.org/10.1378/chest.07-0637.
17. Yoshikawa M, Sukoh N, Yamazaki K, et al. Diagnostic value of endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions without X-ray fluoroscopy. Chest. 2007;131(6):1788–93. https://www.sciencedirect.com/science/article/pii/S0012369215375127. https://doi.org/10.1378/chest.06-2506.
18. Fielding DIK, Robinson PJ, Kurimoto N. Biopsy site selection for endobronchial ultrasound guide-sheath transbronchial biopsy of peripheral lung lesions. Intern Med J. 2008;38(2):77–84. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1445-5994.2007.01473.x. https://doi.org/10.1111/j.1445-5994.2007.01473.x.
19. Chao T, Chien M, Lie C, Chung Y, Wang J, Lin M. Endobronchial ultrasonography-guided transbronchial needle aspiration increases the diagnostic yield of peripheral pulmonary lesions: a randomized trial. Chest. 2009;136(1):229. https://www.ncbi.nlm.nih.gov/pubmed/18812446
20. Lin S, Chung F, Huang C, et al. Diagnostic value of endobronchial ultrasonography for pulmonary tuberculosis. J Thorac Cardiovasc Surg. 2009;138(1):179–84. https://www.clinicalkey.es/playcontent/1-s2.0-S0022522309005200. https://doi.org/10.1016/j.jtcvs.2009.04.004.
21. Haidong H, Yunye N, Wei Z, et al. Multiple guided technologies based on radial probe endobronchial ultrasound for the diagnosis of solitary peripheral pulmonary lesions: a single-center study. J Cancer. 2017;8(17):3514–21. https://www.ncbi.nlm.nih.gov/pubmed/29151936. https://doi.org/10.7150/jca.20035.
22. Ost DE, Ernst A, Lei X, et al. Diagnostic yield and complications of bronchoscopy for peripheral lung lesions. Results of the AQuIRE registry. Am J Respir Crit Care Med. 2016;193(1):68–77. https://www.ncbi.nlm.nih.gov/pubmed/26367186. https://doi.org/10.1164/rccm.201507-1332OC.
23. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest. 2012;142(2):385–93. https://www.clinicalkey.es/playcontent/1-s2.0-S0012369212604516. https://doi.org/10.1378/chest.11-1764.
24. Ali MS, Trick W, Mba BI, Mohananey D, Sethi J, Musani AI. Radial endobronchial ultrasound for the diagnosis of peripheral pulmonary lesions: a systematic review and meta-analysis. Respirology. 2017;22(3):443–53. https://doi.org/10.1111/resp.12980.
25. Steinfort DP, Khor YH, Manser RL, Irving LB. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. Eur Respir J. 2011;37(4):902–10. https://www.ncbi.nlm.nih.gov/pubmed/20693253. https://doi.org/10.1183/09031936.00075310.
26. Steinfort DP, Wurzel D, Irving LB, Ranganathan SC. Endobronchial ultrasound in pediatric pulmonology. Pediatr Pulmonol. 2009;44(4):303–8. https://www.ncbi.nlm.nih.gov/pubmed/19283761. https://doi.org/10.1002/ppul.20991.
27. Chernick V, Kendig EL. Kendig's disorders of the respiratory tract in children. 7th ed. Philadelphia: Saunders Elsevier; 2006.
28. Steinfort D, Irving L. Use of fluoroscopy during endobronchial ultrasonography for transbronchial lung biopsies of peripheral lung lesions. J Thorac Oncol. 2008;3(6):685–6. https://www.openaire.eu/search/publication?articleId=base_oa_____::496d5e1677bc726755db1c6f13bc1851. https://doi.org/10.1097/jto.0b013e3181757b02.
29. Wall BF, Hart D. Revised radiation doses for typical X-ray examinations. Report on a recent review of doses to patients from medical X-ray examinations in the UK by NRPB. National radiological protection board. Br J Radiol. 1997;70(833):437–9. https://www.ncbi.nlm.nih.gov/pubmed/9227222. https://doi.org/10.1259/bjr.70.833.9227222.
30. Kurimoto N, Murayama M, Yoshioka S, Nishisaka T, Inai K, Dohi K. Assessment of usefulness of endobronchial ultrasonography in determination of depth of tracheobronchial tumor invasion. Chest. 1999;115(6):1500–6. https://www.sciencedirect.com/science/article/pii/S0012369215382805. https://doi.org/10.1378/chest.115.6.1500.
31. Tanaka F, Muro K, Yamasaki S, et al. Evaluation of tracheo-bronchial wall invasion using transbronchial ultrasonography (TBUS). Eur J Cardiothorac Surg. 2000;17(5):570–4. https://doi.org/10.1016/S1010-7940(00)00372-9.
32. Wakamatsu T, Tsushima K, Yasuo M, et al. Usefulness of preoperative endobronchial ultrasound for airway invasion around the trachea: Esophageal cancer and thyroid cancer. Respiration. 2006;73(5):651–7. https://www.karger.com/Article/Abstract/93160. https://doi.org/10.1159/000093160.
33. Herth F, Ernst A, Schulz M, Becker H. Endobronchial ultrasound reliably differentiates between airway

infiltration and compression by tumor. Chest. 2003;123(2):458–62. https://www.sciencedirect.com/science/article/pii/S0012369215324569. https://doi.org/10.1378/chest.123.2.458.
34. Miyazu Y, Miyazawa T, Kurimoto N, et al. Endobronchial ultrasonography in the diagnosis and treatment of relapsing polychondritis with tracheobronchial malacia. Chest. 2003;124(6):2393–5. https://www.sciencedirect.com/science/article/pii/S0012369215317062. https://doi.org/10.1378/chest.124.6.2393.
35. Murgu S, Kurimoto N, Colt H. Endobronchial ultrasound morphology of expiratory central airway collapse. Respirology. 2008;13(2):315–9. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1440-1843.2007.01216.x. https://doi.org/10.1111/j.1440-1843.2007.01216.x.
36. Soja J, Grzanka P, Składek K, et al. The use of endobronchial ultrasonography in assessment of bronchial wall remodeling in patients with asthma. Chest. 2009;136(3):797–804. https://www.sciencedirect.com/science/article/pii/S0012369209605493. https://doi.org/10.1378/chest.08-2759.
37. Wang KP, Terry P, Marsh B. Bronchoscopic needle aspiration biopsy of paratracheal tumors. Am Rev Respirat Dis. 1978;118(1):17. https://www.ncbi.nlm.nih.gov/pubmed/677557
38. Mehta AC, Kavuru MS, Meeker DP, Gephardt GN, Nunez C. Transbronchial needle aspiration for histology specimens. Chest. 1989;96(6):1228–32. https://www.sciencedirect.com/science/article/pii/S0012369216393138. https://doi.org/10.1378/chest.96.6.1228.
39. Dasgupta A, Jain P, Minai OA, et al. Utility of transbronchial needle aspiration in the diagnosis of endobronchial lesions. Chest. 1999;115(5):1237–41. https://www.sciencedirect.com/science/article/pii/S0012369215352739. https://doi.org/10.1378/chest.115.5.1237.
40. Oho K, Koto H, Ogawa I, Hayashi N, Hayata Y. A new needle for transfiberoptic bronchoscopic use. Chest. 1979;76(4):492. https://www.sciencedirect.com/science/article/pii/S0012369216398324. https://doi.org/10.1378/chest.76.4.492a.
41. Wang KP, Johns CJ, Fuenning C, Terry PB. Flexible transbronchial needle aspiration for the diagnosis of sarcoidosis. Ann Otol Rhinol Laryngol. 1989;98(4):298–300. https://journals.sagepub.com/doi/full/10.1177/000348948909800412. https://doi.org/10.1177/000348948909800412.
42. White CS, Weiner EA, Patel P, Britt EJ. Transbronchial needle aspiration: guidance with CT fluoroscopy. Chest. 2000;118(6):1630. https://www.ncbi.nlm.nih.gov/pubmed/11115451. https://doi.org/10.1378/chest.118.6.1630.
43. Yasufuku K, Chiyo M, Sekine Y, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration of mediastinal and hilar lymph nodes. Chest. 2004;126(1):122–8. https://www.sciencedirect.com/science/article/pii/S0012369215329044. https://doi.org/10.1378/chest.126.1.122.
44. Yasufuku K, Chiyo M, Koh E, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. Lung Cancer. 2005;50(3):347–54. https://www.sciencedirect.com/science/article/pii/S0169500205003235. https://doi.org/10.1016/j.lungcan.2005.07.013.
45. Herth FJF, Eberhardt R, Vilmann P, Krasnik M, Ernst A. Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax. 2006;61(9):795–8. https://www.ncbi.nlm.nih.gov/pubmed/16738038. https://doi.org/10.1136/thx.2005.047829.
46. Yasufuku K, Nakajima T, Motoori K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. Chest. 2006;130(3):710–8. https://www.sciencedirect.com/science/article/pii/S0012369215527839. https://doi.org/10.1378/chest.130.3.710.
47. Herth FJF, Ernst A, Eberhardt R, Vilmann P, Dienemann H, Krasnik M. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. Eur Respir J. 2006;28(5):910–4. http://erj.ersjournals.com/cgi/content/abstract/28/5/910. https://doi.org/10.1183/09031936.06.00124905.
48. Oki M, Saka H, Kitagawa C, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. Respirology. 2007;12(6):863–8. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1440-1843.2007.01145.x. https://doi.org/10.1111/j.1440-1843.2007.01145.x.
49. Tournoy KG, De Ryck F, Vanwalleghem LR, et al. Endoscopic ultrasound reduces surgical mediastinal staging in lung cancer: a randomized trial. Am J Respir Crit Care Med. 2008;177(5):531–5. http://ajrccm.atsjournals.org/cgi/content/abstract/177/5/531. https://doi.org/10.1164/rccm.200708-1241OC.
50. Ernst A, Anantham D, Eberhardt R, Krasnik M, Herth FJF. Diagnosis of mediastinal adenopathy—real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. J Thorac Oncol. 2008;3(6):577–82. https://www.openaire.eu/search/publication?articleId=base_oa_____::3ff412fdeafab53bd6ccea8158e49a38. https://doi.org/10.1097/jto.0b013e3181753b5e.
51. von Bartheld MB, Dekkers OM, Szlubowski A, et al. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA. 2013;309(23):2457–64. https://doi.org/10.1001/jama.2013.5823.
52. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e211S. https://www.ncbi.nlm.nih.gov/pubmed/23649440
53. Herth FJF, Eberhardt R, Krasnik M, Ernst A. Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal

mediastinum in patients with lung cancer. Chest. 2008;133(4):887–91. https://www.sciencedirect.com/science/article/pii/S0012369215496758. https://doi.org/10.1378/chest.07-2535.
54. Hwangbo B, Kim MS, Kim H, et al. Application of endobronchial ultrasound-guided transbronchial needle aspiration following integrated PET/CT in mediastinal staging of potentially operable non-small cell lung cancer. Chest. 2009;135(5):1280–7. https://www.sciencedirect.com/science/article/pii/S0012369209603081. https://doi.org/10.1378/chest.08-2019.
55. Agarwal R, Srinivasan A, Aggarwal AN, Gupta D. Efficacy and safety of convex probe EBUS-TBNA in sarcoidosis: a systematic review and meta-analysis. Respir Med. 2012;106(6):883–92. https://www.clinicalkey.es/playcontent/1-s2.0-S0954611112000820. https://doi.org/10.1016/j.rmed.2012.02.014.
56. Madan K, Mohan A, Ayub II, et al. Initial experience with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from a tuberculosis endemic population. J Bronchol Intervent Pulmonol. 2014;21(3):208–14. https://www.ncbi.nlm.nih.gov/pubmed/24992128. https://doi.org/10.1097/LBR.0000000000000080.
57. Iqbal S, DePew ZS, Kurtin PJ, et al. Endobronchial ultrasound and lymphoproliferative disorders: a retrospective study. Ann Thorac Surg. 2012;94(6):1830–4. https://www.clinicalkey.es/playcontent/1-s2.0-S0003497512018838. https://doi.org/10.1016/j.athoracsur.2012.08.051.
58. Kennedy MP, Jimenez CA, Bruzzi JF, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. Thorax. 2008;63(4):360–5. https://www.ncbi.nlm.nih.gov/pubmed/17965071. https://doi.org/10.1136/thx.2007.084079.
59. Moonim MT, Breen R, Fields PA, Santis G. Diagnosis and subtyping of de novo and relapsed mediastinal lymphomas by endobronchial ultrasound needle aspiration. Am J Respir Crit Care Med. 2013;188(10):1216. https://www.ncbi.nlm.nih.gov/pubmed/24047336. https://doi.org/10.1164/rccm.201303-0462OC.
60. Senturk A, Babaoglu E, Kilic H, et al. Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. Asian Pac J Cancer Prev. 2014;15(10):4169. https://www.ncbi.nlm.nih.gov/pubmed/24935365
61. Steinfort DP, Conron M, Tsui A, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for the evaluation of suspected lymphoma. J Thorac Oncol. 2010;5(6):804–9. https://www.openaire.eu/search/publication?articleId=base_oa_____::3545782bab1aaf88ccdd67986c870657. https://doi.org/10.1097/jto.0b013e3181d873be.
62. Wahidi M, Herth F, Yasufuku K, et al. Technical aspects of endobronchial ultrasound-guided transbronchial needle aspiration. Chest. 2016;149(3):816–35. https://www.clinicalkey.es/playcontent/1-s2.0-S0012369215000306. https://doi.org/10.1378/chest.15-1216.
63. Eapen GA, Shah AM, Lei X, et al. Complications, consequences, and practice patterns of endobronchial ultrasound-guided transbronchial needle aspiration: results of the AQuIRE registry. Chest. 2013;143(4):1044. https://www.ncbi.nlm.nih.gov/pubmed/23117878. https://doi.org/10.1378/chest.12-0350.
64. Kayawake H, Chen-Yoshikawa TF, Oda H, et al. Complications of endobronchial ultrasound-guided transbronchial needle aspiration. Ann Thorac Surg. 2017;104(5):e365. https://www.sciencedirect.com/science/article/pii/S0003497517308494. https://doi.org/10.1016/j.athoracsur.2017.06.015.
65. Casal RF, Staerkel GA, Ost D, et al. Randomized clinical trial of endobronchial ultrasound needle biopsy with and without aspiration. Chest. 2012;142(3):568–73. https://www.clinicalkey.es/playcontent/1-s2.0-S0012369212604991. https://doi.org/10.1378/chest.11-0692.
66. Yarmus LB, Akulian JA, Gilbert C, et al. Comparison of moderate versus deep sedation for endobronchial ultrasound transbronchial needle aspiration. Ann Am Thorac Soc. 2013;10(2):121. https://www.ncbi.nlm.nih.gov/pubmed/23607840
67. Casal RF, Lazarus DR, Kuhl K, et al. Randomized trial of endobronchial ultrasound-guided transbronchial needle aspiration under general anesthesia versus moderate sedation. Am J Respir Crit Care Med. 2015;191(7):796–803. https://www.ncbi.nlm.nih.gov/pubmed/25574801. https://doi.org/10.1164/rccm.201409-1615OC.
68. Dal T, Sazak H, Tunç M, Sahin S, Yılmaz A. A comparison of ketamine-midazolam and ketamine-propofol combinations used for sedation in the endobronchial ultrasound-guided transbronchial needle aspiration: a prospective, single-blind, randomized study. J Thorac Dis. 2014;6(6):742. https://www.ncbi.nlm.nih.gov/pubmed/24976998. https://doi.org/10.3978/j.issn.2072-1439.2014.04.10.
69. Sarkiss M, Kennedy M, Riedel B, et al. Anesthesia technique for endobronchial ultrasound-guided fine needle aspiration of mediastinal lymph node. J Cardiothorac Vasc Anesth. 2007;21(6):892–6. https://www.clinicalkey.es/playcontent/1-s2.0-S1053077007002935. https://doi.org/10.1053/j.jvca.2007.09.017.
70. DiBardino DM, Haas AR, Month RC. Interventional pulmonology. Anesthesiol Clin. 2017;35(4):687–99. https://www.sciencedirect.com/science/article/pii/S1932227517300897. https://doi.org/10.1016/j.anclin.2017.08.004.
71. McCrone L, Alexander S, Karsli C, et al. US-guided percutaneous needle biopsy of anterior mediastinal masses in children. Pediatr Radiol. 2012;42(1):40–9. https://www.ncbi.nlm.nih.gov/pubmed/21863292. https://doi.org/10.1007/s00247-011-2204-2.
72. Gun F, Toker A, Kaya S, et al. Cervical mediastinoscopy for paratracheal masses in pediatric patients. Pediatr Hematol Oncol. 2008;25(5):393–7. http://www.ingentaconnect.com/content/apl/upho/2008/00000025/00000005/art00003. https://doi.org/10.1080/08880010802104593.
73. Shah R, Reddy AS, Dhende NP. Video assisted thoracic surgery in children. J Minimal Access

Surg. 2007;3(4):161–7. https://www.ncbi.nlm.nih.gov/pubmed/19789677. https://doi.org/10.4103/0972-9941.38910.
74. Massie RJ, Van Asperen PP, Mellis CM. A review of open biopsy for mediastinal masses. J Paediatr Child Health. 1997;33(3):230–3.
75. Hancock BJ, Lorenzo MD, Youssef S, Yazbeck S, Marcotte J, Collin P. Childhood primary pulmonary neoplasms. J Pediatr Surg. 1993;28(9):1133–6. https://www.sciencedirect.com/science/article/pii/002234689390147D. https://doi.org/10.1016/0022-3468(93)90147-D.
76. Hartman GE, Shochat SJ. Primary pulmonary neoplasms of childhood: a review. Ann Thorac Surg. 1983;36(1):108. http://ats.ctsnetjournals.org/cgi/content/abstract/36/1/108
77. Roby BB, Drehner D, Sidman JD. Pediatric tracheal and endobronchial tumors: an institutional experience. Arch Otolaryngol Head Neck Surg. 2011;137(9):925–9. https://doi.org/10.1001/archoto.2011.153.
78. Goussard P, Gie RP, Kling S, et al. The diagnostic value and safety of transbronchial needle aspiration biopsy in children with mediastinal lymphadenopathy. Pediatr Pulmonol. 2010;45(12):1173–9. https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.21303. https://doi.org/10.1002/ppul.21303.
79. Gilbert CR, Feller-Kopman D, Akulian J, Hayes M, Yarmus L. Interventional pulmonology procedures in the pediatric population. Pediatr Pulmonol. 2014;49(6):597–604. https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.22855. https://doi.org/10.1002/ppul.22855.
80. Dhooria S, Madan K, Pattabhiraman V, et al. A multicenter study on the utility and safety of EBUS-TBNA and EUS-B-FNA in children. Pediatr Pulmonol. 2016;51(10):1031–9. https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.23415. https://doi.org/10.1002/ppul.23415.
81. Gilbert CR, Chen A, Akulian JA, et al. The use of convex probe endobronchial ultrasound-guided transbronchial needle aspiration in a pediatric population: a multicenter study. Pediatr Pulmonol. 2014;49(8):807–15. https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.22887. https://doi.org/10.1002/ppul.22887.
82. Wurzel DF, Steinfort DP, Massie J, Ryan MM, Irving LB, Ranganathan SC. Paralysis and a perihilar protuberance: an unusual presentation of sarcoidosis in a child. Pediatr Pulmonol. 2009;44(4):410–4. https://www.ncbi.nlm.nih.gov/pubmed/19283837. https://doi.org/10.1002/ppul.20979.
83. Madan K, Ayub II, Mohan A, Jain D, Guleria R, Kabra SK. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in mediastinal lymphadenopathy. Indian J Pediatr. 2015;82(4):378–80. https://www.ncbi.nlm.nih.gov/pubmed/25567076. https://doi.org/10.1007/s12098-014-1665-3.
84. Siemsen M, Andersen NEO, Nielsen KG. EBUS in a 6-year-old boy with enlarged hilar lymph nodes. J Bronchol Intervent Pulmonol. 2011;18(2):205. https://www.ncbi.nlm.nih.gov/pubmed/23169099. https://doi.org/10.1097/LBR.0b013e31821811e5.
85. Griscom NT, Wohl ME. Dimensions of the growing trachea related to age and gender. Am J Roentgenol. 1986;146(2):233–7. http://www.ajronline.org/cgi/content/abstract/146/2/233. https://doi.org/10.2214/ajr.146.2.233.
86. Tan GM, Tan-Kendrick APA. Bronchial diameters in children–use of the fogarty catheter for lung isolation in children. Anaesth Intensive Care. 2002;30(5):615. https://www.ncbi.nlm.nih.gov/pubmed/12413262
87. Dhooria S, Sehgal IS, Aggarwal AN, Agarwal R. Whither, not wither: Endoscopic ultrasound-guided fine-needle aspiration by an interventional pulmonologist using an echobronchoscope? Chest. 2015;148(3):e100. https://www.sciencedirect.com/science/article/pii/S0012369215506776. https://doi.org/10.1378/chest.15-1121.
88. Medford AR. Endoscopic ultrasound bronchoscope-guided fine needle aspiration (EUS-B-FNA). Thoracic Cancer. 2013;4(1):90. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1759-7714.2012.00168.x. https://doi.org/10.1111/j.1759-7714.2012.00168.x.
89. Leong P, Deshpande S, Irving LB, et al. Endoscopic ultrasound fine-needle aspiration by experienced pulmonologists: a cusum analysis. Eur Respir J. 2017;50(5):1701102. https://www.ncbi.nlm.nih.gov/pubmed/29097432. https://doi.org/10.1183/13993003.01102-2017.
90. Madan K, Garg P, Kabra SK, Mohan A, Guleria R. Transesophageal bronchoscopic ultrasound-guided fine-needle aspiration (EUS-B-FNA) in a 3-year-old child. J Bronchol Intervent Pulmonol. 2015;22(4):347–50. https://www.ncbi.nlm.nih.gov/pubmed/26492608. https://doi.org/10.1097/LBR.0000000000000169.
91. Early DS, Acosta RD, Chandrasekhara V, et al. Adverse events associated with EUS and EUS with FNA. Gastrointest Endosc. 2013;77(6):839–43. https://www.clinicalkey.es/playcontent/1-s2.0-S0016510713001764. https://doi.org/10.1016/j.gie.2013.02.018.
92. Qin C, Wei B, Ma Z. Endobronchial ultrasound: echoing in the field of pediatrics. Endosc Ultrasound. 2018; https://www.ncbi.nlm.nih.gov/pubmed/30289110
93. Wada H, Hirohashi K, Nakajima T, et al. Assessment of the new thin convex probe endobronchial ultrasound bronchoscope and the dedicated aspiration needle: a preliminary study in the porcine lung. J Bronchol Intervent Pulmonol. 2015;22(1):20–7. https://www.ncbi.nlm.nih.gov/pubmed/25590479. https://doi.org/10.1097/LBR.0000000000000123.
94. Patel P, Wada H, Hu H, et al. First evaluation of the new thin convex probe endobronchial ultrasound scope: a human ex vivo lung study. Ann Thorac Surg. 2017;103(4):1158–64. https://www.clinicalkey.es/playcontent/1-s2.0-S0003497516312747. https://doi.org/10.1016/j.athoracsur.2016.09.023.

Electromagnetic Navigational Bronchoscopy

36

Julio E. Noriega and Pi Chun Cheng

Introduction

Small peripheral pulmonary lesions (PPLs) are increasingly identified on cross-sectional imaging. The differential diagnosis of lung nodules includes infection, malignancy, or an inflammatory process. Computed tomography (CT)–guided biopsy is a common method to biopsy lung lesions. Despite the high diagnostic yield, the rate of pneumothorax by CT-guided biopsy has been reported to be up to 42% with approximately 6% requiring chest tube insertion. Risk factors for pneumothorax include pre-existing cystic or bullous lung disease [1, 2]. Additional considerations against the use of CT-guided biopsy include the presence of a single lung or comorbidities limiting the ability to tolerate an iatrogenic pneumothorax.

Alternatively, conventional flexible bronchoscopy can be used to locate lesions in the bronchial tree. Bronchoscopy is also the safest and least-invasive method of lung nodule biopsy by avoiding the complications of pleural and chest wall puncture. This is particularly important because a minimally invasive bronchoscopic approach can decrease the risk of respiratory decompensation in medically complex pediatric patients. However, nodules located in the peripheral third of the lung are beyond the subsegmental bronchi and cannot generally be reached with conventional bronchoscopy. The ability to direct the bronchoscope to the periphery of the lung and do so accurately, safely, and reliably has become more achievable through the use of electromagnetic navigational bronchoscopy (ENB). The use of ENB has been prioritized and utilized primarily in the adult population. This is due to the higher incidence of pulmonary malignancies [3, 4], either primary or metastatic, that require sampling (Fig. 36.1). Although the incidence of malignant pulmonary nodules in children is lower than in adults [5], the advantages of bronchoscopic biopsy remain. In the pediatric population, bacterial, fungal, and atypical infections are common causes of lung nodules, masses, and cavities [6]. Safe tissue sampling can assist in establishing a diagnosis, differentiate between malignant, infectious, or other causes, and provide pathologic and microbiologic material for identification and laboratory analysis. At present, there are no published pediatric reports using ENB in the literature. Data that supports indications for the use of ENB, diagnostic yield, and complication rates

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_36

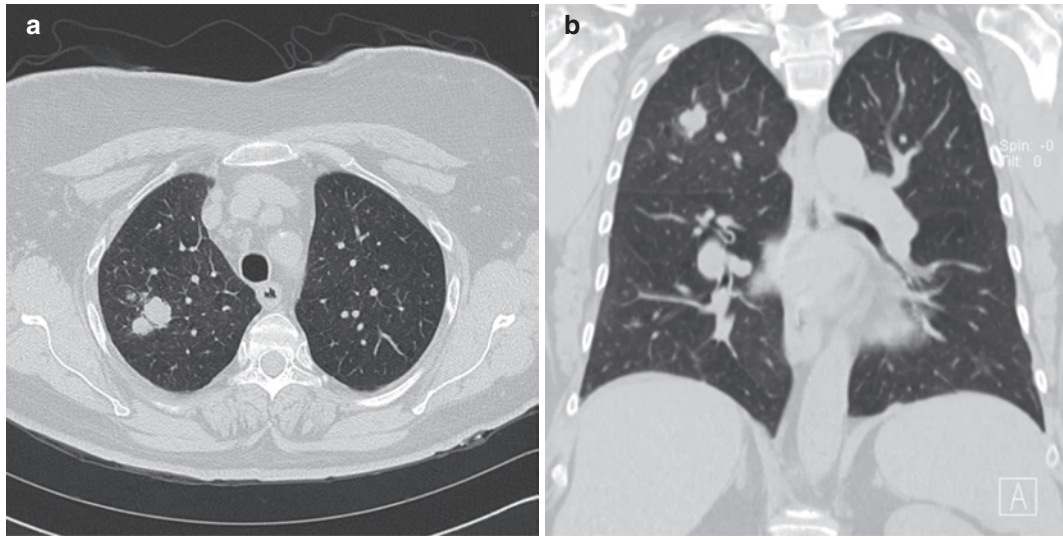

Fig. 36.1 Axial (**a**) and coronal (**b**) computed tomographic images of a right upper lobe nodule in the periphery of the lung successfully biopsied by electromagnetic navigational bronchoscopy

exists solely based on the adult population. In this chapter, we will discuss the general methodology of ENB, review the relevant literature, and discuss its potential use in the pediatric population.

Virtual Bronchoscopy

The precursor of ENB is virtual bronchoscopy (VB). It is the reconstruction of a CT image to create a three-dimensional image of the airways from the viewpoint of a bronchoscope. In and of itself, it is not an invasive procedure. In virtual bronchoscopic navigation, the VB image can be displayed concomitantly to a conventional bronchoscopic image to inform the proceduralist of the airway path that leads to the target lesion. Their combined use has been shown to improve yields in PPL biopsy [7]. However, there is no real-time information as to where the bronchoscope is located in the tracheobronchial tree. VB provided the base from which more advanced ENB techniques were created. This has been used in the pediatric population as an adjunct diagnostic tool to fiberoptic bronchoscopy [8].

Electromagnetic Navigational Bronchoscopy

Once a CT image of the thorax could be reconstructed to simulate the bronchoscopic view through the airway tree, a method of locating and guiding an instrument with a locator guide (LG) through the airways in real-time became feasible. ENB uses an electromagnetic field created around the thorax of the patient to detect where in the airway tree an LG is located. The main ENB platforms available in the United States are the superDimension™ (Medtronic, Minneapolis, MN), the SPiN Thoracic Navigation System™ (Veran, Saint Louis, MO), and the Archimedes™ (Broncus, San Jose, CA). The following generally describes the superDimension™ platform as it was the first FDA-approved system for ENB.

Planning is the process where the CT images of the thorax are reconstructed into a three-dimensional bronchoscopic view and a virtual pathway to the lesion is created for the bronchoscope to follow. For superDimension™, the manufacturer recommends using an inspiratory scan with thin cuts (1–1.25 mm) and 20–50% overlap as optimal CT scan and reconstruction parameters [9]. Once uploaded, the software will

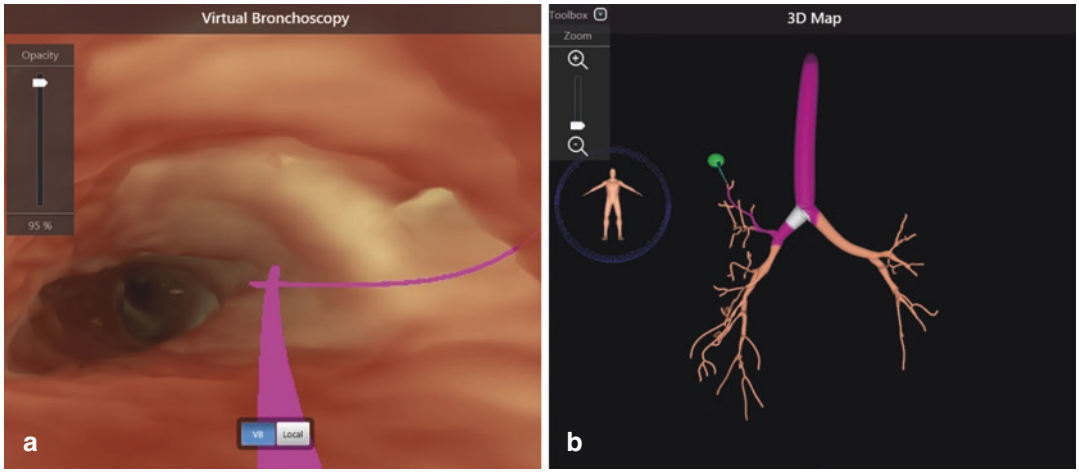

Fig. 36.2 Planning view of the superDimension™ platform used to biopsy the nodule in Fig. 36.1 showing (**a**) the virtual bronchoscopy image with the planned airway course (pink) and (**b**) the airway reconstruction with path to the target lesion (green sphere) through the posterior segment of the right upper lobe. (*Courtesy Christopher Manley, Fox Chase Cancer Center*)

then identify the image series that is the closest to specifications. The bronchoscopist will select the series to be processed and the VB image will be generated. The target is then identified on the CT scan and the VB image. The software creates an airway path to the target lesion and, after review or editing by the bronchoscopist, the pathway is saved. This data is saved and imported onto the procedure station. The patient is then laid supine over an electromagnetic location board encompassing the entire thorax. This board creates an electromagnetic field wherein the LG is identified. Once adequate anesthesia is achieved, the bronchoscope with the LG is inserted into the patient's airways.

Registration refers to the process of synchronizing the LG to identifiable landmarks of the VB image. Typically, the bronchoscope with the LG is advanced to the carina and both mainstem bronchi. Registration can be performed automatically or manually, and there are differences in the registration process among manufacturer's systems. Once registration is completed, the VB image appears on the system. From here, navigation to the target lesion begins. The bronchoscope with an extended working channel (EWC) and LG is advanced with guidance from the planned airway path until the bronchoscope wedges in a segmental or subsegmental airway that is leading to the target lesion. The EWC with the LG is then advanced to the target lesion using directionally curved (Edge™) catheters that can be rotated to the proper orientation and advanced. This is done under guidance from the navigation software, beyond the bronchoscopist's visual view. Once the catheter is at the target lesion, the LG is removed and the EWC is locked in place. Proper placement can be further evaluated by using a radial probe-endobronchial ultrasound (r-EBUS), discussed below. A combination of r-EBUS and fluoroscopy can confirm that the EWC is directed toward the target lesion and the biopsy can then be performed. The EWC can accommodate biopsy needles, brushes, or forceps. Once specimens are obtained, the EWC is removed [10] (Fig. 36.2).

Robotic Bronchoscopy

Robotic bronchoscopy is thus far the most advanced method in bronchoscopic peripheral lung biopsy. This procedure builds on all of the previous modalities discussed and incorporates robotic handling of the bronchoscope

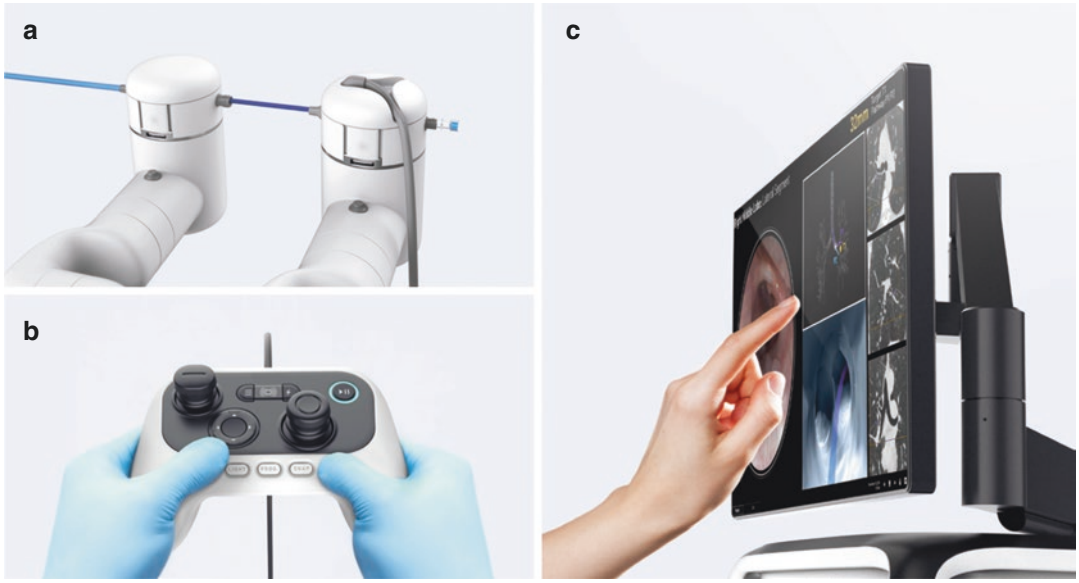

Fig. 36.3 The Monarch™ (**a**) control arms advance and rotate a flexible bronchoscope directed by a separate controller (**b**). The procedure platform carries a touchscreen for visualization and navigation screens (**c**). (*Courtesy Auris Health*)

to the target lesion. The bronchoscopist controls the robotic handling of a bronchoscope using a separate controller. A feasibility study in 2018 showed that the Robotic Endoscopy System (Auris Surgical Robotics, San Carlos, CA) was able to successfully navigate to PPLs in 17 patients [11]. There are currently two robotic bronchoscopy platforms available: the Monarch™ (Auris Health, Redwood City, CA) and the Ion™ (Intuitive Surgical, Sunnyvale, CA) (Fig. 36.3). Compared to manual guidance, the use of robotic guidance allows for precise millimeter-by-millimeter movements in the desired direction and continued maintenance of an endobronchial view to the target lesion. The bronchoscope is also constantly locked in position unless specifically moved, reducing inadvertent backtracking (Fig. 36.4). Compared to conventional thin bronchoscopes, robotic systems have improved reach into the lung periphery [12]. The BENEFIT study (ClinicalTrials.gov: NCT03727425) is ongoing to determine the rate of adverse events and successful navigation to the target. To date, there are no published reports of the use of robotic bronchoscopy in children.

Anesthesia

The method of anesthesia among centers that perform ENB is variable. Considerations in selecting the level of anesthesia include the availability of personnel and resources. In the United States, the first trial used conscious sedation [13], which many centers continue to use. General anesthesia has an advantage of allowing paralysis of the patient to eliminate patient movement and cough. Difficulty in achieving an appropriate level of sedation due to tolerance to opioids or benzodiazepines is also reduced. However, there are no differences in yield reported with the use of either method of anesthesia, though the duration of the procedure is significantly longer with general anesthesia [14].

Fluoroscopy

Most facilities use single-plane fluoroscopy. If the target lesion is visible on fluoroscopy, its use is greatly beneficial. However, with the superDimension system, the fluoroscopic c-arm cannot be used during the actual navigation as it creates

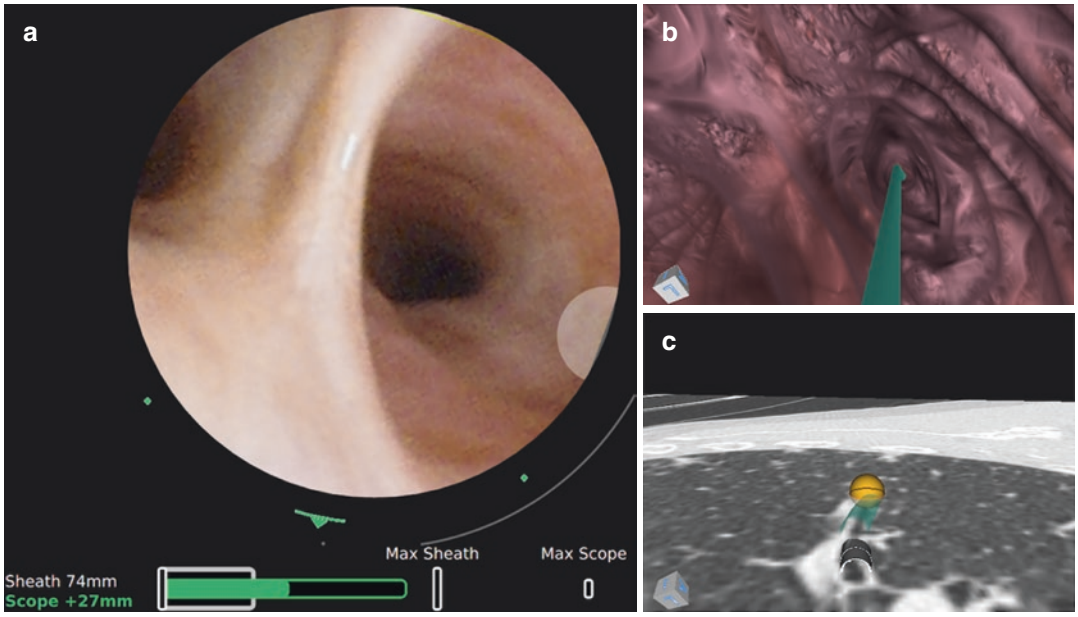

Fig. 36.4 Navigation view of the Monarch™ bronchoscopy platform showing (**a**) visualization of the airway, (**b**) virtual bronchoscopy image with the airway path (green), and (**c**) the CT-image showing the locator guide in the bronchus leading to the target lesion (yellow). (*Courtesy Christopher Manley, Fox Chase Cancer Center*)

ferromagnetic interference, rendering real-time navigation inaccurate. The c-arm is brought onto the field once navigation is completed to visualize the course and position of the EWC. It can be activated during the biopsy to visualize the sampling and ensure consistent positioning. Because there is generally no direct visualization of the target lesion during ENB, fluoroscopy represents the only live observation of the instrumentation of the lung, and we recommend its use.

Radial Probe Endobronchial Ultrasound

Radial probe endobronchial ultrasound (r-EBUS) can be used to assess whether the EWC is directed toward the target lesion by the visualization of a hypoechoic signal of the approximate size and shape of the target lesion (Fig. 36.5). It was originally developed as a diagnostic tool for identification of peripheral nodules, but without navigation system guidance, it leads to the need for repeated and often random insertions into different bronchi in hopes of identifying the target. Its disadvantages include the inability to directly visualize what is in front of the probe, only what is around it, and that it has to be removed during biopsy; therefore visualization is not in real time. A study with 118 patients directly compared the

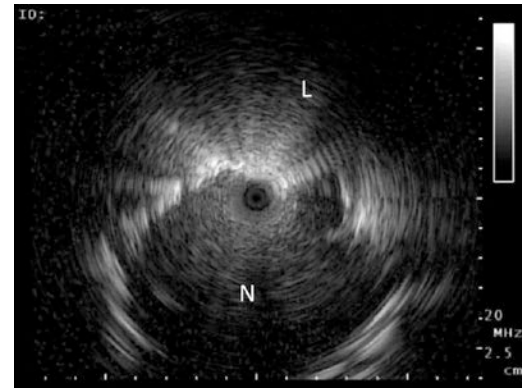

Fig. 36.5 Radial probe endobronchial ultrasound of the lesion in Fig. 36.1 showing the probe on the periphery of a hypoechoic nodule (N) with surrounding aerated lung (L)

use of ENB alone, radial EBUS alone, and with combined ENB and radial EBUS. The diagnostic yield was highest when both modalities were used together (59% vs 69% vs 88%) [15].

Rapid On-Site Evaluation

Rapid on-site evaluation (ROSE) of cytopathologic material allows for the analysis of the aspirate immediately after acquisition. The presence of abnormal cells thus confirms correct positioning. It has been shown to increase diagnostic yield [16, 17]. This practice is helpful in the diagnosis of malignancy and less so for infections without specific cytologic features [18].

Diagnostic Yield

To date, there have been three published meta-analyses on the role of ENB in diagnosing PPLs. Wang Memoli et al. included 39 studies with a total of 3,004 patients with pulmonary lung nodules. The pooled diagnostic yield of ENB was found to be 70% [19]. Gex et al. included 15 trials with a total of 971 patients with peripheral lung nodules. Overall diagnostic yield was found to be 73.9% [20]. Zhang et al. looked at a total of 17 studies consisting of 1,106 patients with PPLs. They found a sensitivity of 82% and specificity of 100%, the diagnostic yield ranged from 60% to 94% [21]. The majority of studies listed in these three meta-analyses are small, single centered, and were done by expert operators [19–21]. The meta-analyses noted possible selection bias as ENB could have been chosen in more difficult cases where conventional techniques were not suitable, leading to a lower diagnostic yield. The NAVIGATE trial is a multicenter prospective cohort study of the use of ENB with the superDimension navigation system for PPLs. A recent one-year result of a US cohort of 1215 patients showed a diagnostic yield of 73% [22]. The diagnostic yield of ENB is affected by several factors. Larger lesions and upper lobe location increase the yield [21, 23, 24]. The bronchus sign, where a bronchus is visible on CT leading directly into a PPL, is also associated with increased diagnostic yield (Fig. 36.6) [25, 26]. Fluoroscopy was used in 91% of cases, though the lesion was visible by fluoroscopy in only 60% of cases [22]. Radial probe EBUS was used in 57% of cases [22]. Due to its overall reasonable safety profile and diagnostic yield, adult lung cancer guidelines recommend ENB in patients with peripheral lung lesions which are difficult to reach with conventional bronchoscopy, provided that both expertise and equipment are available [27, 28].

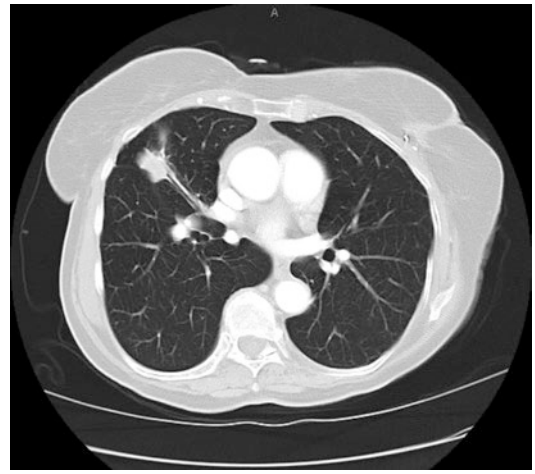

Fig. 36.6 A bronchus sign arising from the lateral segment of the right middle lobe into a pulmonary nodule. The presence of a bronchus sign is associated with a higher diagnostic yield than if the bronchus is simply adjacent to or at a distance away from the lesion

Complications

Despite being the most common serious complication, the risk of pneumothorax with ENB is several times lower than that of CT-guided percutaneous biopsy. Recent meta-analyses publish a rate ranging from 1.5% to 4.9% [19, 20, 29]. While risk factors for pneumothorax specific to ENB are not elucidated, previous data from transbronchial biopsy and transthoracic needle aspiration likely applies. These include closer distance to the peripheral or interlobar pleura, small nodules, and the presence of emphysema or bullae [30, 31].

The risk of clinically significant bleeding is rare in ENB. In the NAVIGATE trial, the incidence of grade ≥2 bronchopulmonary hemorrhage was 1.5% [22]. The bronchoscope

is typically wedged into a subsegmental airway during biopsy which acts as a tamponade. The appearance of a new opacity on fluoroscopy can act as a warning that bleeding has occurred.

Limitations

Despite sophisticated navigational software and positioning systems, there are several limitations to ENB. There are inevitably some differences between CT-based virtual images compared to the patient's actual anatomy. This leads to misregistration of the LG by the navigation software. There are some areas of the lungs that are simply difficult to be reached with a flexible bronchoscope, and successful navigation is limited by the catheter curvatures. There is also the possibility that the EWC is dislodged from the locked position during tissue biopsy. Additionally, the procedure yield is highly dependent on the experience of the operator, and there is a steep learning curve. One previous contraindication unique to ENB was in the setting of cardiac pacemakers and defibrillators. However, a study of 24 patients with pacemakers and defibrillators who underwent ENB reported that none of the patients suffered arrhythmia and that the procedure was safely completed [32]. Finally, the cost of the procedure can be prohibitive. ENB is an expensive technique with a substantial investment in the initial setup of the equipment, continued use of disposable components, and training of the skilled personnel.

Therapeutic Uses of ENB

There has been an expanded role of not only biopsy but also performing interventions on PPLs using ENB. In adults, fiducial placement assists in guiding radiation therapy and has been performed via CT-guided approach as well as bronchoscopically. ENB allows for bronchoscopic fiducial placement while avoiding the complications of CT-guided pleural puncture [33]. Interstitial brachytherapy involves the placement of a radiation source directly into a tumor to provide radiation therapy. ENB with interstitial brachytherapy was well tolerated in a prospective feasibility trial [34]. In a prospective study of 18 patients with localized lung cancer and were inoperable, no significant complications were observed and complete remission was noted in 50% of patients who were treated [35].

Future Directions

Currently, ENB is not FDA approved in the pediatric population. Nevertheless, the need of safe tissue sampling of lung nodules and lesions certainly exists in the pediatric population. This is especially important in medically complex and fragile children where open lung biopsy may not be suitable due to significant associated risk. ENB may serve as an alternative approach to diagnosis and possibly even treatment with targeted therapy in the future. Further investigation is needed to identify the diagnostic yield and safety profile of ENB in the pediatric population.

Conclusion

ENB is a technology that allows safe tissue biopsy from PPLs that are traditionally difficult to biopsy using conventional bronchoscopy. ENB can be used alone or in combination with r-EBUS and fluoroscopy to biopsy nodules. Robotic bronchoscopy may further push the boundaries of ENB. While ENB is not widely utilized in the pediatric population, application of this technology may lead to diagnosis and treatment of many lesions previously unable to be identified. Future studies are needed to demonstrate the utility and safety of ENB in the pediatric population.

References

1. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. Ann Intern Med. 2011;155:137–44.
2. Hiraki T, Mimura H, Gobara H, Shibamoto K, Inoue D, Matsui Y, Kanazawa S. Incidence of and risk factors for pneumothorax and chest tube placement after CT fluoroscopy-guided percutaneous lung

biopsy: retrospective analysis of the procedures conducted over a 9-year period. AJR Am J Roentgenol. 2010;194:809–14.
3. Higgins GA, Shields TW, Keehn RJ. The solitary pulmonary nodule. Ten-year follow-up of veterans administration-armed forces cooperative study. Arch Surg. 1975;110:570–5.
4. Chan EY, Gaur P, Ge Y, Kopas L, Santacruz JF, Gupta N, Munden RF, Cagle PT, Kim MP. Management of the Solitary Pulmonary Nodule. Arch Pathol Lab Med. 2017;141:927–31.
5. Neville HL, Hogan AR, Zhuge Y, Perez EA, Cheung MC, Koniaris LG, Thompson WR, Sola JE. Incidence and outcomes of malignant pediatric lung neoplasms. J Surg Res. 2009;156:224–30.
6. Ashraf SF, Lau KKW. Navigation bronchoscopy: a new tool for pulmonary infections. Med Mycol. 2019;57:S287–93.
7. Miyoshi S, Isobe K, Shimizu H, Sunakawa M, Suzuki A, Sugino K, Shiraga N, Sakamoto S, Takai Y, Iyoda A, et al. The utility of virtual bronchoscopy using a computed tomography workstation for conducting conventional bronchoscopy: a retrospective analysis of clinical practice. Respiration. 2019;97:52–9.
8. Konen E, Katz M, Rozenman J, Ben-Shlush A, Itzchak Y, Szeinberg A. Virtual bronchoscopy in children: early clinical experience. AJR Am J Roentgenol. 1998;171:1699–702.
9. Medtronic C. Recommended CT scan and Reconstruction Parameters SuperDimension Planning Station Version 7.0. http://www.superdimension.com/.
10. Gildea TR, Anciano CJ. Electromagnetic navigation bronchoscopy. In: Mehta AC, Jain P, editors. Interventional bronchoscopy; a clinical guide. New York City, NY: Humana Press; 2013. p. 107–20.
11. Rojas-Solano JR, Ugalde-Gamboa L, Machuzak M. Robotic bronchoscopy for diagnosis of suspected lung cancer: a feasibility study. J Bronchol Interv Pulmonol. 2018;25:168–75.
12. Chen AC, Gillespie CT. Robotic endoscopic airway challenge: REACH assessment. Ann Thorac Surg. 2018;106:293–7.
13. Gildea TR, Mazzone PJ, Karnak D, Meziane M, Mehta AC. Electromagnetic navigation diagnostic bronchoscopy: a prospective study. Am J Respir Crit Care Med. 2006;174:982–9.
14. Bowling MR, Kohan MW, Walker P, Efird J, Ben Or S. The effect of general anesthesia versus intravenous sedation on diagnostic yield and success in electromagnetic navigation bronchoscopy. J Bronchol Interv Pulmonol. 2015;22:5–13.
15. Eberhardt R, Anantham D, Ernst A, Feller-Kopman D, Herth F. Multimodality bronchoscopic diagnosis of peripheral lung lesions: a randomized controlled trial. Am J Respir Crit Care Med. 2007;176:36–41.
16. Lamprecht B, Porsch P, Pirich C, Studnicka M. Electromagnetic navigation bronchoscopy in combination with PET-CT and rapid on-site cytopathologic examination for diagnosis of peripheral lung lesions. Lung. 2009;187:55–9.
17. Balbo PE, Bodini BD, Patrucco F, Della Corte F, Zanaboni S, Bagnati P, Andorno S, Magnani C. Electromagnetic navigation bronchoscopy and rapid on site evaluation added to fluoroscopy-guided assisted bronchoscopy and rapid on site evaluation: improved yield in pulmonary nodules. Minerva Chir. 2013;68:579–85.
18. Wilson DSB, Rebecca. Improved diagnostic yield of bronchoscopy in a community practice: combination of electromagnetic navigation system and rapid on-site evaluation. J Bronchol. 2007;14:227–32.
19. Wang Memoli JS, Nietert PJ, Silvestri GA. Meta-analysis of guided bronchoscopy for the evaluation of the pulmonary nodule. Chest. 2012;142:385–93.
20. Gex G, Pralong JA, Combescure C, Seijo L, Rochat T, Soccal PM. Diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules: a systematic review and meta-analysis. Respiration. 2014;87:165–76.
21. Zhang W, Chen S, Dong X, Lei P. Meta-analysis of the diagnostic yield and safety of electromagnetic navigation bronchoscopy for lung nodules. J Thorac Dis. 2015;7:799–809.
22. Folch EE, Pritchett MA, Nead MA, Bowling MR, Murgu SD, Krimsky WS, Murillo BA, LeMense GP, Minnich DJ, Bansal S, et al. Electromagnetic navigation bronchoscopy for peripheral pulmonary lesions: one-year results of the prospective, multicenter NAVIGATE study. J Thorac Oncol. 2019;14:445–58.
23. Jensen KW, Hsia DW, Seijo LM, Feller-Kopman DJ, Lamb C, Berkowitz D, Curran-Everett D, Musani AI. Multicenter experience with electromagnetic navigation bronchoscopy for the diagnosis of pulmonary nodules. J Bronchol Interv Pulmonol. 2012;19:195–9.
24. Chen A, Pastis N, Furukawa B, Silvestri GA. The effect of respiratory motion on pulmonary nodule location during electromagnetic navigation bronchoscopy. Chest. 2015;147:1275–81.
25. Ali MS, Sethi J, Taneja A, Musani A, Maldonado F. Computed tomography bronchus sign and the diagnostic yield of guided bronchoscopy for peripheral pulmonary lesions. A systematic review and meta-analysis. Ann Am Thorac Soc. 2018;15:978–87.
26. Seijo LM, de Torres JP, Lozano MD, Bastarrika G, Alcaide AB, Lacunza MM, Zulueta JJ. Diagnostic yield of electromagnetic navigation bronchoscopy is highly dependent on the presence of a Bronchus sign on CT imaging: results from a prospective study. Chest. 2010;138:1316–21.
27. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e142S–65S.
28. Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, Wiener RS. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e93S–e120S.

29. Khandhar SJ, Bowling MR, Flandes J, Gildea TR, Hood KL, Krimsky WS, Minnich DJ, Murgu SD, Pritchett M, Toloza EM, et al. Electromagnetic navigation bronchoscopy to access lung lesions in 1,000 subjects: first results of the prospective, multicenter NAVIGATE study. BMC Pulm Med. 2017;17:59.
30. Khan MF, Straub R, Moghaddam SR, Maataoui A, Gurung J, Wagner TO, Ackermann H, Thalhammer A, Vogl TJ, Jacobi V. Variables affecting the risk of pneumothorax and intrapulmonal hemorrhage in CT-guided transthoracic biopsy. Eur Radiol. 2008;18:1356–63.
31. Chino H, Iikura M, Saito N, Sato N, Suzuki M, Ishii S, Morino E, Naka G, Takasaki J, Izumi S, et al. Subinterlobular pleural location is a risk factor for pneumothorax after bronchoscopy. Respir Care. 2016;61:1664–70.
32. Khan AY, Berkowitz D, Krimsky WS, Hogarth DK, Parks C, Bechara R. Safety of pacemakers and defibrillators in electromagnetic navigation bronchoscopy. Chest. 2013;143:75–81.
33. Bolton WD, Richey J, Ben-Or S, Hale AL, Ewing JA, Stephenson JE. Electromagnetic navigational bronchoscopy: a safe and effective method for fiducial marker placement in lung cancer patients. Am Surg. 2015;81:659–62.
34. Harms W, Krempien R, Grehn C, Hensley F, Debus J, Becker HD. Electromagnetically navigated brachytherapy as a new treatment option for peripheral pulmonary tumors. Strahlenther Onkol. 2006;182:108–11.
35. Becker HDea. Brachytherapy of inoperable peripheral lung cancer guided by electromagnetic navigation and endobronchial ultrasound: feasibility study and confirmation by long-term results at two centers. Chest. 2009;134:2S.

Endobronchial Valves

37

Jennifer W. Toth and Michael F. Reed

Background

Chronic obstructive pulmonary disease (COPD) affects millions of people. Advanced emphysema results in severe breathlessness and is a leading cause of mortality. Smoking cessation, oxygen treatment, and noninvasive ventilation can decrease mortality [1]. In the mid-twentieth century, the concept of lung volume reduction surgery (LVRS) was proposed [2]. With resection, plication, or decompression of the emphysematous lung, relief of dyspnea, and improved exercise tolerance would occur by diminished thoracic distention, improved respiratory mechanics, and redirection of inspired volume to more preserved lung parenchyma. Cooper and colleagues [3] introduced surgical bilateral lung volume reduction in a series of 20 patients, demonstrating improved mean forced expiratory volume in 1 second (FEV_1) and reduced total lung capacity, residual volume, and air trapping. The changes were associated with relief of dyspnea, improved exercise tolerance, and better quality of life. Cooper's results, and other reports that followed, led to the National Emphysema Treatment Trial (NETT) which evaluated 3777 patients with severe COPD, enrolling 1218 patients, of whom 608 were randomly assigned to LVRS (by median sternotomy or video-assisted thoracoscopic surgery) and 610 to medical therapy [4]. After the exclusion of a high-risk group, LVRS significantly improved survival, quality of life, and exercise capacity. The greatest benefit was to patients with heterogenous emphysema and low exercise capacity.

While the NETT demonstrated that lung volume reduction was effective, LVRS was associated with 5% mortality, as well as 20% and 30% incidences of major pulmonary and cardiac morbidity, respectively [5]. The NETT also identified a particularly high-risk group of patients, those with FEV_1 less than 20% of predicted and either homogenous emphysema or a carbon monoxide diffusion capacity (D_LCO) less than 20% of predicted, in whom 30-day mortality after LVRS was 16% [4].

Safer approaches than LVRS, directed toward achieving the physiologic benefits with less morbidity and mortality, subsequently emerged. Many postulated that blocking an airway supplying hyperinflated emphysematous regions of lung could collapse these areas, thereby alleviating symptoms in those with severe emphysema [6]. A variety of interventions were proposed,

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_37

including bronchoscopic placement of endobronchial blockers or valves, injection of fibrin polymer into emphysematous lung parenchyma, and creating stented transbronchial pathways between cartilaginous airways and emphysematous lung [1]. Pilot studies of endobronchial valves showed positive results, including safety, radiographic evidence of regional lung volume reduction, improved quality of life, and increased FEV_1. Two randomized multicenter trials of endobronchial valves (LIBERATE trial of the Zephyr Endobronchial Valve [EBV], Pulmonyx Corporation and EMPROVE trial of the Spiration Valve System [SVS], Olympus) have led to their approval by FDA for the treatment of severe emphysema [7, 8].

Endobronchial valves for lung volume reduction were designed to redirect airflow away from emphysematous lung, toward the less-diseased lung parenchyma. Early in endobronchial valve development, it was recognized that the goal of redirecting ventilation could also be an effective and minimally invasive method for a different clinical problem—prolonged air leak. The valves could reduce airflow through leaking tissue, allowing healing with the resolution of the air leak [9].

Alveolopleural Fistula

Alveolopleural fistula is defined as an abnormal communication between the lung parenchyma and the pleural space [10]. This results in a pneumothorax. Placement of a chest tube drains the air. The tube should be attached to a drainage system, such as a three-compartment system, a one-way (Heimlich) valve for ambulatory drainage, or a digital system [11–13]. The three-compartment systems, now integrated disposable units, permit the adjustment of negative pressure or no suction (water seal), and include an air leak meter on the water seal chamber to be used for observing and quantifying the air leak. The air leak can be described as expiratory, inspiratory, continuous, or forced expiratory, while the number of chambers on the meter demonstrating bubbles can quantify the degree of air leak [14]. These readings are prone to subjectivity and variability between observers. Digital pleural drainage systems offer the benefits of quantification of the air leak and pleural pressure [13].

Most pneumothoraces, particularly primary spontaneous pneumothoraces, resolve with tube thoracostomy drainage. However, some air leaks may persist more than 5–7 days, indicative of a prolonged air leak.

Incidence and Risk Factors for Prolonged Air Leak

Air leaks are common after surgical pulmonary resection, occurring in the majority of cases, but self-limiting in most [15]. The incidence of prolonged air leak after pulmonary resection has been reported from 3% to over 25% [10, 15–19]. Within 30 days after LVRS in the NETT, 90% developed air leak at some point, with a median duration of 7 days, and 12% experienced an air leak persisting at 30 days [20]. Notably, air leak after pulmonary surgery is associated with more complications and longer length of hospital stay. In adults, risk factors for prolonged air leak after pulmonary surgery include COPD, low FEV_1, low D_LCO, pleural adhesions, smoking history, chronic steroid use, and diabetes mellitus [10, 16, 17, 20]. In particular, underlying pulmonary disease, including emphysema, interstitial lung disease, sarcoidosis, and radiation fibrosis, predisposes to prolonged air leak [21]. An air leak that is present on the fourth postoperative day portends an 83% chance it will persist to day seven [21].

Pneumothorax during mechanical ventilation, an especially worrisome presentation of alveolopleural fistula, is a significant complication associated with poor prognosis. Outcomes are particularly grim when the pneumothorax results in a prolonged air leak [10]. Lung-protective strategies to minimize pneumothorax can therefore directly improve patient outcomes.

In children, prolonged air leak (as in the adult population) can occur in the postoperative setting, as well as after spontaneous pneumothorax, with necrotizing infectious processes leading to

fistulae, and during mechanical ventilation (volutrauma from high tidal volumes and barotrauma from high peak airway pressures) [22–26]. In a study of 80 critically ill children admitted to a pediatric intensive care unit with ARDS, pneumonia, asthma, congenital pulmonary disease, foreign body aspiration, and bronchiolitis, increased mortality was associated with prolonged air leaks on mechanical ventilation, especially with multisystem organ failure, sepsis, and pulmonary superinfection with Pseudomonas or Candida species [26]. Positive end-expiratory pressure (PEEP) did not differ between the air leak and non-air leak groups, suggesting that the etiology was volutrauma. The air leak incidence was 27.5% (one or several episodes), with a greater frequency in children with congenital abnormalities, ARDS, or foreign body aspiration. Median time to air leak development was 2 days after the initiation of mechanical ventilation, and treatment was with tube thoracostomy. Subsequently, the children with air leaks had a longer duration of mechanical ventilation, hospital stay, and overall mortality. Deaths were due to complications associated with sepsis.

The incidence of spontaneous pneumothorax in children is estimated at 3.4 cases per 100,000 [27]. There is a bimodal distribution, occurring in the neonatal period and later adolescence, especially in boys with a tall, thin body habitus. Spontaneous pneumothoraces are caused by tears in the visceral pleura due to rupture of subpleural blebs, either congenital or acquired [28]. Diagnoses associated with secondary spontaneous pneumothoraces in children include cystic fibrosis, Marfan's syndrome, bronchopulmonary dysplasia, and asthma. Prolonged air leak is more common for secondary spontaneous pneumothorax. As with adults [29–31], surgical intervention using video-assisted thoracoscopic surgery (VATS) should be considered at the initial presentation of secondary spontaneous pneumothorax in children due to the high rate of prolonged air leak and a significant recurrence rate [27, 28, 32]. In addition to wedge resection or bullectomy, a pleural intervention (pleural abrasion, pleurectomy, and/or chemical pleurodesis) should be considered to lower the risk of recurrence [33, 34]. Spontaneous pneumothorax, primary or secondary, associated with a prolonged air leak should be managed surgically. However, the optimal management children with an initial presentation of primary spontaneous pneumothorax and prompt resolution of the air leak is less defined. While some children are effectively treated nonoperatively with pleural drainage on the first occurrence of primary spontaneous pneumothorax, the majority will ultimately recur, warranting surgical intervention [27, 35]. Many therefore recommend VATS with bullectomy and pleural intervention for children at an initial presentation of primary spontaneous pneumothorax [27, 35, 36].

Management of Prolonged Air Leak

Prolonged air leak from spontaneous pneumothorax should be managed surgically with VATS wedge resection/bullectomy and a pleural intervention in most cases. Chemical or autologous blood pleurodesis (blood patch) is an alternative intervention, typically considered for patients who are poor surgical candidates or those who refuse an operative procedure [10]. Similarly, chemical pleurodesis or blood patch can be used for prolonged air leak occurring after thoracic surgery.

Autologous blood pleurodesis can be performed via a chest tube [37–42]. The patient's blood is instilled into the pleural space, allowing for sealing of the air leak while avoiding toxic substances. It is inexpensive and easy to perform, and has been effectively utilized in pediatric patients [43, 44]. In a study [43] involving spontaneous pneumothoraces in 29 pediatric patients, 5 received autologous blood pleurodesis with 50 milliliters of autologous blood, with the resolution of the air leak in a median of 2.6 days. One patient needed a repeat blood patch for a persistent air leak, and one other had an ipsilateral pneumothorax recurrence after the blood patch. Notably, all patients were at elevated risk for surgery: 2 had prior VATS bullectomy and pleurodesis and 3 had postoperative prolonged air leak (1 after VATS bullectomy and 2 after lung

transplantation). The use of autologous blood pleurodesis should occur in a monitored setting, especially in the situation of a prolonged air leak, where tube occlusion with clot can result in tension pneumothorax. Placement of the thoracostomy tubing over an intravenous pole allows the blood to remain in the pleural space while still allowing air egress. Flushing with saline toward and away from the patient prevents clot formation [40, 44–46].

Chemical pleurodesis through a chest tube is a well-established technique for the management of malignant pleural effusion, especially for patients who are at high risk for surgery. In the setting of postoperative prolonged air leak, sclerosis with talc, bleomycin, doxycycline, and minocycline has been effective [19, 41, 47]. Yet there remain concerns about the safety, particularly the risk of ARDS, associated with talc pleurodesis [48].

Reoperative surgical intervention for a postoperative prolonged air leak can be effective, but may carry significant risk. Patients with postoperative prolonged air leak usually have significant risk factors predisposing to air leak that decrease the likelihood of success with reoperation, they have often already failed interventions through a chest tube, and they can be debilitated after recently undergoing thoracic surgery. Surgical reintervention may not be amenable to minimally invasive surgery by VATS and thus require thoracotomy. Surgical intervention can include restapling, anatomic resection such as lobectomy, use of topical sealants, or obliteration of residual pleural space with omentum or muscle flaps [9, 41]. Moreover, reoperative surgery is not always successful, and can occasionally worsen the air leak by injury to fragile lungs.

Many of the reports of surgical treatment or instillation of blood or sclerosant through a chest tube for prolonged air leak, whether postoperative or spontaneous, are anecdotal, single-institutional experience, not randomized, or include heterogenous indications. There is also limited substantive evidence that they consistently result in earlier resolution of air leak [9]. Thus, minimally invasive methods have been sought for the management of prolonged air leak. Bronchoscopic approaches have been attempted for years with the goal of localizing the airways contributing to the leak and introducing a substance or device to occlude them. Localization is commonly performed with a balloon catheter though the bronchoscope, observing the air leak in the integrated three-compartment drainage system [49] or digital air leak monitor [50]. The airways contributing to the leak can then be occluded with glues or adhesives (fibrin, albumin, glutaraldehyde, polyethylene glycol-gel, hydrogel, cyanoacrylates), cellulose and autologous blood, ethanol, ethanolamine, antibiotics, silver nitrate, decalcified spongy calf bone, stents, lead shot, coils, or Watanabe spigots [9, 49, 51–56]. In children, a limited number of these interventions have also been employed [57]. A 2005 review focusing on endoscopic management of bronchopleural fistula noted that none of the aforementioned endobronchial interventions reproducibly eliminated air leak. The lack of consensus on the best endoscopic approach suggested that no optimal therapy was available [51].

Endobronchial Valve Management of Prolonged Air Leak

Endobronchial valves were initially developed for lung volume reduction, achieved by redirecting airflow away from emphysematous lung, toward the less-diseased lung parenchyma. It was soon recognized that the valves could reduce airflow through leaking lung tissue, offering a minimally invasive treatment for prolonged air leak [9].

Case reports using endobronchial valves for prolonged air leaks began appearing in 2005 [9, 58–60]. Most were for patients at high risk for surgery and the etiologies for the prolonged air leaks were varied. Travaline and colleagues [21] compiled a case series of 40 subjects at 17 institutions treating prolonged air leak with endobronchial valves. Again, the etiologies for the prolonged air leak were varied. With the isolation of the airways contributing to the leak and then occlusion with endobronchial valves, 48% achieved complete air leak resolution and 45% had partial resolution. Gillespie and colleagues [61] reported 8 endobronchial valve placement procedures for

prolonged air leak where the median duration of leakage was 4 weeks before and 1 day after treatment, with discharge in 2–3 days of the procedure in 57% of patients. Two endobronchial valve systems, the Emphasys bronchial valve (precursor to the Zephyr Endobronchial Valve) and the Spiration Valve System, received approval for marketing in the European Union, with approval granted for treating emphysema and prolonged air leak. In the United States, the Spiration Valve System received FDA approval for the treatment of prolonged air leak after surgical lobectomy, segmentectomy, or lung volume reduction under the Humanitarian Device Exemption program.

A key procedural component in managing prolonged air leaks using endobronchial valves is demonstrating diminished air leak with balloon bronchial occlusion. Firlinger and colleagues [50] showed that a digital air leak monitor attached to the chest tube can effectively assess air leak before, during, and after the valve implantation. The Leuven team [62] reported that early use of endobronchial valves for prolonged air leak after anatomic lung resection for cancer, with the aid of a digital thoracic drainage system, resulted in air leak cessation a median of 2 days after valve placement and chest tube removal a median of 4 days after valve placement.

With endobronchial valves proven effective for prolonged air leak resulting from pulmonary resection, a number of larger series examined their efficacy in challenging clinical scenarios resulting in prolonged air leak [63–65]. In medically compromised patients with prolonged air leak from a variety of conditions, both postoperative and spontaneous pneumothoraces in clinical settings that included severe COPD, ARDS, ongoing oncologic treatment, and severe pulmonary infection, endobronchial valve placement facilitated the resolution of air leak and subsequent chest tube removal.

Prolonged air leak is also a significant challenge in children. Toth and colleagues [66] reported the experience of an interdisciplinary team of pediatric surgeons, pediatric intensivists, interventional pulmonologists, and thoracic surgeons who treated a series of four children (16 months to 16 years) with refractory air leaks using endobronchial valves. Two had air leaks following necrotizing pneumonia, one following lobectomy and one from a pneumatocele. Chest tubes had been present up to 76 days before endobronchial valve placement. All four children had complete resolution of air leaks, all were discharged from the hospital, and none required additional surgery.

Two endobronchial valve systems are currently available in the United States, indicated for prolonged air leak after surgical lung resection and for bronchoscopic lung volume reduction for emphysema. The Spiration Valve System (Spiration, Inc., Redmond, WA; Olympus America) is an umbrella-shaped self-expanding device with a Nitinol (nickel-titanium) frame with 5 distal anchors and a polyurethane membrane held by six proximal struts (Fig. 37.1). When deployed, the membrane is in apposition to the bronchial wall, thereby allowing the unidirectional valve to block air from travelling distally, while allowing secretions and air to drain (Fig. 37.2). A central stabilizing rod can be used for removal. The Zephyr Endobronchial Valve

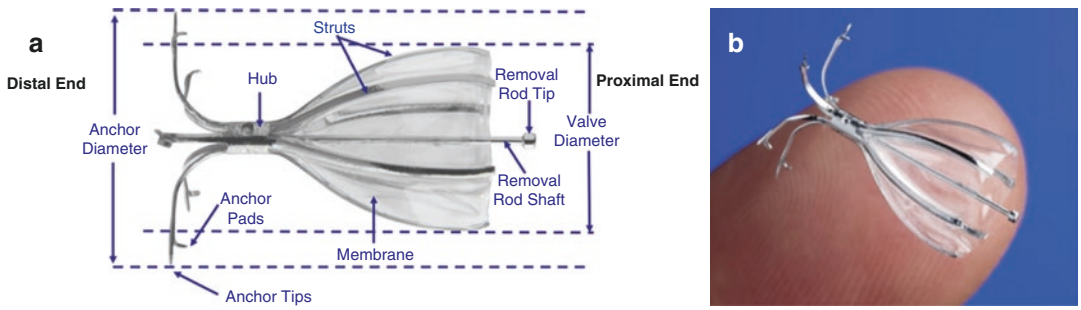

Fig. 37.1 Spiration Valve System. (**a**) Diagram. (**b**) Valve shown to scale

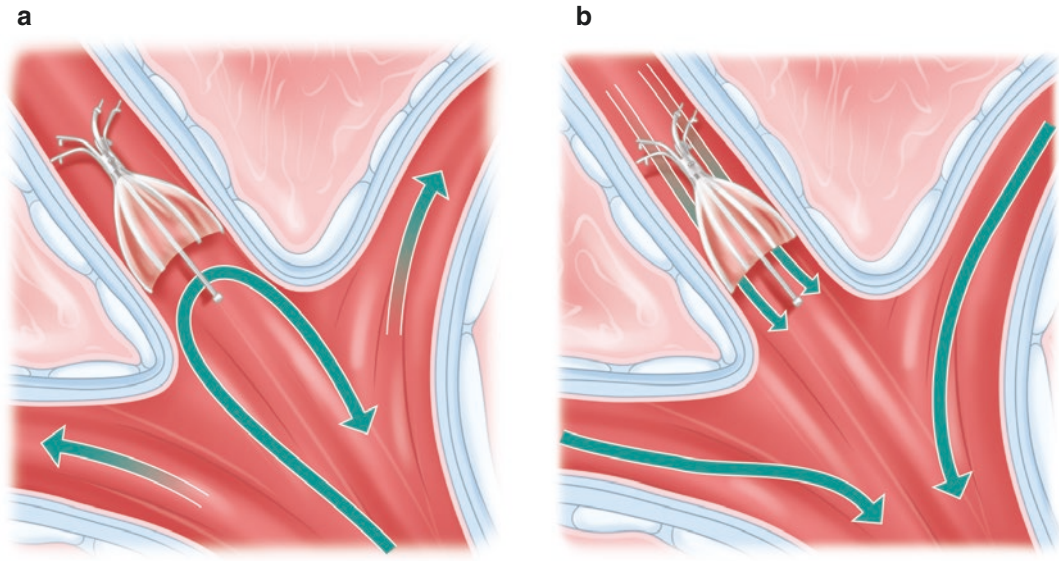

Fig. 37.2 Schematic of airflow redirection by Spiration Valve System. (**a**) Inhalation. (**b**) Exhalation

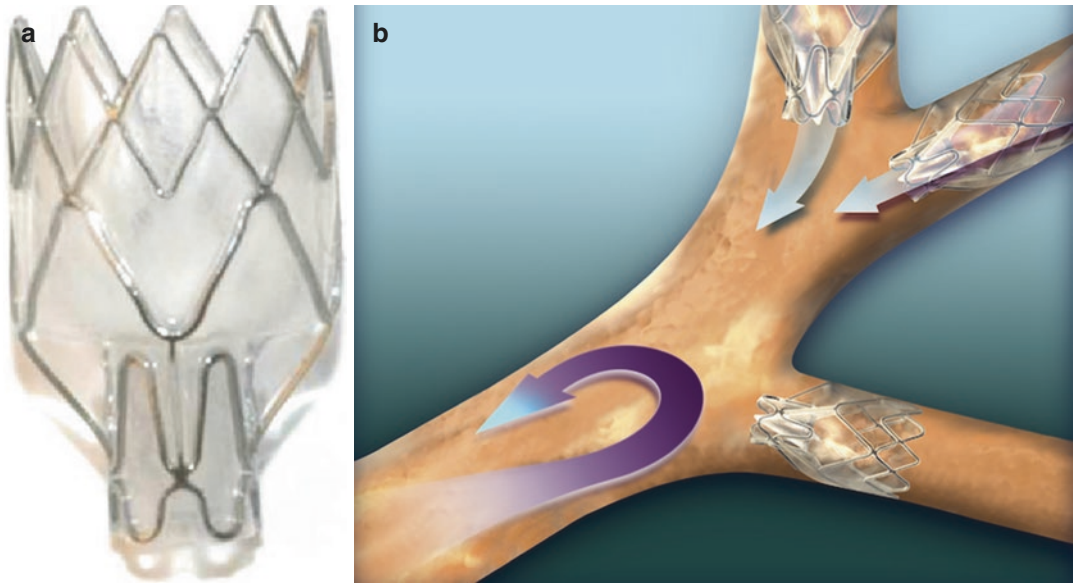

Fig. 37.3 Zephyr Endobronchial Valve. (**a**) One-way valve. (**b**) Schematic of airflow redirection

(Pulmonyx Corporation, Redwood City, CA) is constructed with a silicone-based, one-way valve mounted in a self-expanding nitinol retainer. The retainer stabilizes the valve in the airway and provides an airtight seal against the bronchial wall (Fig. 37.3).

The necessary steps for valve placement are air leak isolation, airway sizing, and valve deployment [67]. Prior to valve implantation for air leaks, a chest drainage system is attached to the chest tube to monitor the air leak. Both integrated three-component pleural drainage systems

and digital air leak monitoring are effective. The anesthetic approach varies among institutions, but many advocate general anesthesia to facilitate the control of ventilation pressure to demonstrate the air leak and to decrease procedure duration. The procedure is most often performed with flexible bronchoscopy (working channel of greater than or equal to 2.6 mm) via a laryngeal mask airway or an endotracheal tube. The air leak is located by balloon occlusion, taking into account imaging and (if present) prior surgical details. Initially, the system is tested by complete occlusion of the ipsilateral main bronchus to verify that the air leak resolves. If not, the system must be evaluated for an external leak originating at the skin, in the tubing and connections, or within the drainage system. A balloon-tipped catheter is then used to selectively occlude airways with continued monitoring of the air leak. Occasionally, two balloons are used (one placed beside the scope if needed) to ascertain air leak origin. Decrease or elimination of the leak indicates that the occluded airway is contributing to the alveolopleural fistula. An increase in the leak signifies an airway that is NOT contributing and therefore shunting air through the fistula. When the air leak has diminished or stopped with balloon occlusion, that specific airway is sized with the accompanying sizing balloon and measurement kit to determine which size valve to deploy. The most distal contributing airways involved are preferred for valve placement in order to preserve as much lung parenchyma as possible. The appropriately sized valve is loaded into the catheter and then deployed under direct (bronchoscopic) visualization. Typically, several endobronchial valves are placed to achieve a significantly diminished or eliminated air leak. After the procedure, the patient is allowed to recover as usual from anesthesia. Weaning from positive pressure ventilation can further diminish the leak.

On occasion the air leak does not completely resolve after the procedure, but diminishes to the point that water seal of the chest drainage system is achieved. In this instance, a one-way ambulatory drainage system (Heimlich valve) can be attached to the chest tube, permitting discharge from the hospital and later chest tube removal at air leak cessation. Such patients are discharged to home with routine chest tube care and emptying of the collection device as needed. Follow-up occurs in the outpatient setting where the device is submerged under water to determine whether air leak is still present, and the tube is removed after the confirmation of air leak resolution. Occasionally a "clamp trial" may be useful. In this case the chest tube is clamped for a few hours to verify that the patient remains stable without ongoing pleural drainage. Some will obtain plain chest radiography during the clamp trial to assure that there is no enlarging pneumothorax. When endobronchial valves are placed for prolonged air leak, they are ideally removed at approximately 6 weeks after chest tube removal using standard bronchoscopy forceps.

With children, certain modifications to the standard technique used in adults may be useful. Toth's team has utilized a tapered adult hybrid bronchoscope (BF-MP160F, Olympus America, Center Valley, PA) in two children for initial identification of the affected airways using the balloon occlusion of the bronchial segments contributing to the fistula [66]. An adult therapeutic bronchoscope was then used for endobronchial valve deployment. In smaller children, where an adult therapeutic bronchoscope with a 2.6 mm or larger working channel cannot fit through the endotracheal tube or airways, the valve can be delivered using a smaller (e.g., hybrid) bronchoscope running parallel to the valve delivery catheter. The catheter can be directed into the appropriate airway, and the valve can be deployed under bronchoscopic visualization. This approach is difficult when the targeted airway requires flexion of the bronchoscope (for example, an upper lobe bronchus). In these cases, forceps through the working channel of the bronchoscope can be used to "guide" the valve into the airway if technically feasible.

Summary

Prolonged air leak resulting from surgery or pneumothorax is associated with a high rate of complications and longer hospital stay. The

affected patients often have significant medical comorbidities that make surgical intervention high risk. Many of the surgical treatments, as well as instillation of blood or sclerosant through chest tubes, have limited substantive evidence that they consistently result in earlier resolution of air leak. One-way endobronchial valves were initially designed as a minimally invasive means to achieve lung volume reduction for emphysema. They are also effective for treating prolonged air leak. In children, where prolonged air leak after surgery or spontaneous pneumothorax is also a clinical challenge, endobronchial valves offer a minimally invasive option for eliminating air leak, facilitating chest tube removal and earlier hospital discharge without the need for additional surgical intervention. Although randomized clinical trials are lacking, several case series reports support safety and efficacy in the pediatric population.

References

1. Sterman DH, Mehta AC, Wood DE, Mathur PN, McKenna RJ Jr, Ost DE, et al. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. Respiration. 2010;79(3):222–33.
2. Brantigan OC, Mueller E, Kress MB. A surgical approach to pulmonary emphysema. Am Rev Respir Dis. 1959;80(1, Part 2):194–206.
3. Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MS, Deloney PA, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg. 1995;109(1):106–16. discussion 16-9
4. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med. 2003;348(21):2059–73.
5. Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, DeCamp MM, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg. 2006;82(2):431–43.
6. Toma TP, Hopkinson NS, Hillier J, Hansell DM, Morgan C, Goldstraw PG, et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet. 2003;361(9361):931–3.
7. Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, Wiese T, et al. A multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). Am J Respir Crit Care Med. 2018;198(9):1151–64.
8. Criner GJ, Delage A, Voelker KG, EMPROVE Trial Investigator Group, editors. The EMPROVE trial – a randomized controlled multicenter clinical study to evaluate the safety and effectiveness of the Spiration® Valve System for single lobe treatment of severe emphysema. American Thoracic Society; 2018; San Diego, CA. Am J Respir Crit Care Med. 2018;197:A7753.
9. Wood DE, Cerfolio RJ, Gonzalez X, Springmeyer SC. Bronchoscopic management of prolonged air leak. Clin Chest Med. 2010;31(1):127–33.
10. Dugan KC, Laxmanan B, Murgu S, Hogarth DK. Management of persistent air leaks. Chest. 2017;152(2):417–23.
11. Zisis C, Tsirgogianni K, Lazaridis G, Lampaki S, Baka S, Mpoukovinas I, et al. Chest drainage systems in use. Ann Transl Med. 2015;3(3):43.
12. McKenna RJ Jr, Fischel RJ, Brenner M, Gelb AF. Use of the Heimlich valve to shorten hospital stay after lung reduction surgery for emphysema. Ann Thorac Surg. 1996;61(4):1115–7.
13. Cerfolio RJ, Varela G, Brunelli A. Digital and smart chest drainage systems to monitor air leaks: the birth of a new era? Thorac Surg Clin. 2010;20(3):413–20.
14. Cerfolio RJ, Bass C, Katholi CR. Prospective randomized trial compares suction versus water seal for air leaks. Ann Thorac Surg. 2001;71(5):1613–7.
15. Okereke I, Murthy SC, Alster JM, Blackstone EH, Rice TW. Characterization and importance of air leak after lobectomy. Ann Thorac Surg. 2005;79(4):1167–73.
16. Stolz AJ, Schutzner J, Lischke R, Simonek J, Pafko P. Predictors of prolonged air leak following pulmonary lobectomy. Eur J Cardiothorac Surg. 2005;27(2):334–6.
17. Brunelli A, Monteverde M, Borri A, Salati M, Marasco RD, Fianchini A. Predictors of prolonged air leak after pulmonary lobectomy. Ann Thorac Surg. 2004;77(4):1205–10. discussion 10
18. Abolhoda A, Liu D, Brooks A, Burt M. Prolonged air leak following radical upper lobectomy: an analysis of incidence and possible risk factors. Chest. 1998;113(6):1507–10.
19. Liberman M, Muzikansky A, Wright CD, Wain JC, Donahue DM, Allan JS, et al. Incidence and risk factors of persistent air leak after major pulmonary resection and use of chemical pleurodesis. Ann Thorac Surg. 2010;89(3):891–7. discussion 7-8
20. DeCamp MM, Blackstone EH, Naunheim KS, Krasna MJ, Wood DE, Meli YM, et al. Patient and surgical factors influencing air leak after lung volume reduction surgery: lessons learned from the National Emphysema Treatment Trial. Ann Thorac Surg. 2006;82(1):197–206; discussion −7.
21. Travaline JM, McKenna RJ Jr, De Giacomo T, Venuta F, Hazelrigg SR, Boomer M, et al. Treatment of persistent pulmonary air leaks using endobronchial valves. Chest. 2009;136(2):355–60.

22. McKee AJ, Ives A, Balfour-Lynn IM. Increased incidence of bronchopulmonary fistulas complicating pediatric pneumonia. Pediatr Pulmonol. 2011;46(7):717–21.
23. Vianello A, Arcaro G, Gallan F, Ori C, Bevilacqua M. Pneumothorax associated with long-term non-invasive positive pressure ventilation in Duchenne muscular dystrophy. Neuromuscul Disord. 2004;14(6):353–5.
24. Hsieh YC, Wang CW, Lai SH, Lai JY, Wong KS, Huang YC, et al. Necrotizing pneumococcal pneumonia with bronchopleural fistula among children in Taiwan. Pediatr Infect Dis J. 2011;30(9):740–4.
25. Sawicki GS, Lu FL, Valim C, Cleveland RH, Colin AA. Necrotising pneumonia is an increasingly detected complication of pneumonia in children. Eur Respir J. 2008;31(6):1285–91.
26. Briassoulis GC, Venkataraman ST, Vasilopoulos AG, Sianidou LC, Papadatos JH. Air leaks from the respiratory tract in mechanically ventilated children with severe respiratory disease. Pediatr Pulmonol. 2000;29(2):127–34.
27. Williams K, Oyetunji TA, Hsuing G, Hendrickson RJ, Lautz TB. Spontaneous pneumothorax in children: national management strategies and outcomes. J Laparoendosc Adv Surg Tech A. 2018;28(2):218–22.
28. O'Lone E, Elphick HE, Robinson PJ. Spontaneous pneumothorax in children: when is invasive treatment indicated? Pediatr Pulmonol. 2008;43(1):41–6.
29. MacDuff A, Arnold A, Harvey J, British Thoracic Society Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65(Suppl 2):ii18–31.
30. Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. Chest. 2001;119(2):590–602.
31. Sahn SA, Heffner JE. Spontaneous pneumothorax. N Engl J Med. 2000;342(12):868–74.
32. Dotson K, Johnson LH. Pediatric spontaneous pneumothorax. Pediatr Emerg Care. 2012;28(7):715–20. quiz 21–3
33. Sudduth CL, Shinnick JK, Geng Z, McCracken CE, Clifton MS, Raval MV. Optimal surgical technique in spontaneous pneumothorax: a systematic review and meta-analysis. J Surg Res. 2017;210:32–46.
34. Joharifard S, Coakley BA, Butterworth SA. Pleurectomy versus pleural abrasion for primary spontaneous pneumothorax in children. J Pediatr Surg. 2017;52(5):680–3.
35. Lopez ME, Fallon SC, Lee TC, Rodriguez JR, Brandt ML, Mazziotti MV. Management of the pediatric spontaneous pneumothorax: is primary surgery the treatment of choice? Am J Surg. 2014;208(4):571–6.
36. Seguier-Lipszyc E, Elizur A, Klin B, Vaiman M, Lotan G. Management of primary spontaneous pneumothorax in children. Clin Pediatr (Phila). 2011;50(9):797–802.
37. Robinson CL. Autologous blood for pleurodesis in recurrent and chronic spontaneous pneumothorax. Can J Surg. 1987;30(6):428–9.
38. Dumire R, Crabbe MM, Mappin FG, Fontenelle LJ. Autologous "blood patch" pleurodesis for persistent pulmonary air leak. Chest. 1992;101(1):64–6.
39. Chambers A, Routledge T, Bille A, Scarci M. Is blood pleurodesis effective for determining the cessation of persistent air leak? Interact Cardiovasc Thorac Surg. 2010;11(4):468–72.
40. Manley K, Coonar A, Wells F, Scarci M. Blood patch for persistent air leak: a review of the current literature. Curr Opin Pulm Med. 2012;18(4):333–8.
41. Shrager JB, DeCamp MM, Murthy SC. Intraoperative and postoperative management of air leaks in patients with emphysema. Thorac Surg Clin. 2009;19(2):223–31. ix
42. Lang-Lazdunski L, Coonar AS. A prospective study of autologous 'blood patch' pleurodesis for persistent air leak after pulmonary resection. Eur J Cardiothorac Surg. 2004;26(5):897–900.
43. Jimenez Arribas P, Lain Fernandez A, Guillen Burrieza G, Lopez-Fernandez S, Moreno Galdo A, Lloret Roca J. Autologous blood pleurodesis for treatment of spontaneous pneumothorax and persistent air leak in pediatric patients. Cir Pediatr. 2016;29(1):4–7.
44. Pathak V, Quinn C, Zhou C, Wadie G. Use of autologous blood patch for prolonged air leak in spontaneous pneumothoraces in the adolescent population. Lung India. 2018;35(4):328–31.
45. Rinaldi S, Felton T, Bentley A. Blood pleurodesis for the medical management of pneumothorax. Thorax. 2009;64(3):258–60.
46. Lillegard JB, Kennedy RD, Ishitani MB, Zarroug AE, Feltis B. Autologous blood patch for persistent air leak in children. J Pediatr Surg. 2013;48(9):1862–6.
47. How CH, Tsai TM, Kuo SW, Huang PM, Hsu HH, Lee JM, et al. Chemical pleurodesis for prolonged postoperative air leak in primary spontaneous pneumothorax. J Formos Med Assoc. 2014;113(5):284–90.
48. Brant A, Eaton T. Serious complications with talc slurry pleurodesis. Respirology. 2001;6(3):181–5.
49. Watanabe Y, Matsuo K, Tamaoki A, Kamato R, Hiraki S. Bronchial occlusion with endobronchial Watanabe spigot. J Bronchol. 2003;10:264–7.
50. Firlinger I, Stubenberger E, Muller MR, Burghuber OC, Valipour A. Endoscopic one-way valve implantation in patients with prolonged air leak and the use of digital air leak monitoring. Ann Thorac Surg. 2013;95(4):1243–9.
51. Lois M, Noppen M. Bronchopleural fistulas: an overview of the problem with special focus on endoscopic management. Chest. 2005;128(6):3955–65.
52. Mehta HJ, Malhotra P, Begnaud A, Penley AM, Jantz MA. Treatment of alveolar-pleural fistula with endobronchial application of synthetic hydrogel. Chest. 2015;147(3):695–9.
53. Wiaterek G, Lee H, Malhotra R, Shepherd W. Bronchoscopic blood patch for treatment of per-

sistent alveolar-pleural fistula. J Bronchol Interv Pulmonol. 2013;20(2):171–4.
54. Takaoka K, Inoue S, Ohira S. Central bronchopleural fistulas closed by bronchoscopic injection of absolute ethanol. Chest. 2002;122(1):374–8.
55. Lim AL, Kim CH, Hwang YI, Lee CY, Choi JH, Shin T, et al. Bronchoscopic ethanolamine injection therapy in patients with persistent air leak from chest tube drainage. Tuberc Respir Dis (Seoul). 2012;72(5):441–7.
56. Watanabe S, Watanabe T, Urayama H. Endobronchial occlusion method of bronchopleural fistula with metallic coils and glue. Thorac Cardiovasc Surg. 2003;51(2):106–8.
57. Hathorn C, Armitage N, Wensley D, Seear M. Bronchial balloon occlusion in children with complex pulmonary air leaks. Arch Dis Child. 2013;98(2):136–40.
58. Snell GI, Holsworth L, Fowler S, Eriksson L, Reed A, Daniels FJ, et al. Occlusion of a broncho-cutaneous fistula with endobronchial one-way valves. Ann Thorac Surg. 2005;80(5):1930–2.
59. Ferguson JS, Sprenger K, Van Natta T. Closure of a bronchopleural fistula using bronchoscopic placement of an endobronchial valve designed for the treatment of emphysema. Chest. 2006;129(2):479–81.
60. Toma TP, Kon OM, Oldfield W, Sanefuji R, Griffiths M, Wells F, et al. Reduction of persistent air leak with endoscopic valve implants. Thorax. 2007;62(9):830–3.
61. Gillespie CT, Sterman DH, Cerfolio RJ, Nader D, Mulligan MS, Mularski RA, et al. Endobronchial valve treatment for prolonged air leaks of the lung: a case series. Ann Thorac Surg. 2011;91(1):270–3.
62. Dooms CA, Decaluwe H, Yserbyt J, De Leyn P, Van Raemdonck D, Ninane V. Bronchial valve treatment for pulmonary air leak after anatomical lung resection for cancer. Eur Respir J. 2014;43(4):1142–8.
63. Reed MF, Gilbert CR, Taylor MD, Toth JW. Endobronchial valves for challenging air leaks. Ann Thorac Surg. 2015;100(4):1181–6.
64. Gilbert CR, Casal RF, Lee HJ, Feller-Kopman D, Frimpong B, Dincer HE, et al. Use of one-way intrabronchial valves in air leak management after tube thoracostomy drainage. Ann Thorac Surg. 2016;101(5):1891–6.
65. Podgaetz E, Andrade RS, Zamora F, Gibson H, Dincer HE. Endobronchial treatment of bronchopleural fistulas by using intrabronchial valve system: a case series. Semin Thorac Cardiovasc Surg. 2015;27(2):218–22.
66. Toth JW, Podany AB, Reed MF, Rocourt DV, Gilbert CR, Santos MC, et al. Endobronchial occlusion with one-way endobronchial valves: a novel technique for persistent air leaks in children. J Pediatr Surg. 2015;50(1):82–5.
67. Mahajan AK, Doeing DC, Hogarth DK. Isolation of persistent air leaks and placement of intrabronchial valves. J Thorac Cardiovasc Surg. 2013;145(3):626–30.

Whole-Lung Lavage

38

Christopher Towe and Bruce Trapnell

Introduction

Whole-lung lavage (WLL) is a therapeutic procedure performed to facilitate clearance of material from the lung. The use of therapeutic WLL has been reported in diseases such as lipoid pneumonia [1] and pneumoconiosis [2], but the most frequent indication for therapeutic WLL is pulmonary alveolar proteinosis (PAP). Pediatric pulmonologists should be familiar with the indications for and understand the basic concepts of performing the procedure because when indicated and performed properly the benefits of WLL to the patient are dramatic.

PAP occurs rarely in adult patients and is even more rare in pediatric patients. Therefore, WLL is performed infrequently, even at the busiest and most experienced pediatric centers. There have been few studies on the different approaches to WLL in adults, none in pediatrics, and no standardization of approach across centers. WLL requires significant preparation along with close collaboration and communication between the physician performing the lavage, their assistants, and the anesthesia team to produce the safest and most beneficial outcome for the patient. This review of the procedure and description of the techniques used at our center are meant as a general overview but should not be considered comprehensive.

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Pulmonary Alveolar Proteinosis

PAP is a syndrome which occurs when normal surfactant metabolism and homeostasis are disrupted resulting in the buildup of surfactant and surfactant metabolites in the alveoli [3]. Surfactant reduces the surface tension at the air-liquid interface within the alveoli and is made up of lipids (~90%) and proteins (~10%). Surfactant is produced by alveolar type II epithelial cells and cleared either through uptake and recycling by alveolar type II cells or uptake and catabolism by alveolar macrophages.

Overall, the most common cause of PAP is the development of autoimmune antibodies against granulocyte-monocyte colony-stimulating factor (GM-CSF). The interruption of GM-CSF signaling results in alveolar macrophage dysfunction and inability to properly catabolize surfactant and clear it from the alveoli. While most commonly occurring in adults, there are reports of autoimmune PAP occurring in children as young as 6. Hereditary PAP occurs either when there is a mutation in one of the two protein chains that form the GM-CSF receptor

S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_38

[4] or when there is a mutation in a gene critical for surfactant or alveolar macrophage production: surfactant protein B, surfactant protein C, ATP-binding cassette subfamily A member 3 (ABCA3), NK2 Homeobox 1 (NKX2–1), and GATA-binding factor 2 (GATA2) [5]. Secondary PAP has been reported in conditions such as myelodysplastic syndrome [6], patients taking immunosuppressive medications following solid organ transplant [7], and patients who have inhaled certain pulmonary irritants [8, 9].

The presentation of PAP varies depending on the underlying etiology. Autoimmune PAP and PAP secondary to mutations in the GM-CSF receptor typically present with the insidious development of dyspnea. In young children, behavioral changes and/or failure to thrive are sometimes the initial manifestations. Physical exam findings include diminished breath sounds, but clubbing is uncommon. Chest radiographs demonstrate a diffuse bilateral opacification (Fig. 38.1a). Computed tomography (CT) of the chest demonstrates a diffuse ground-glass opacification, that may be patchy, often superimposed on a reticular pattern referred to as "crazy paving" (Fig. 38.2).

Flexible bronchoscopy with bronchoalveolar lavage (BAL) can be diagnostic of PAP, via cytological findings, and useful for excluding infections, but BAL analysis cannot determine the underlying etiology for the PAP. BAL fluid from PAP patients is frequently turbid with a "potato soup" appearance resulting from the extracellular lipid (Fig. 38.3). Determining the etiology underlying the PAP requires specific testing for GM-CSF autoantibodies, genetic testing for hereditary causes, and ruling out other specific causes of secondary PAP as appropriate. Surgical lung biopsy is sometimes, but not always, necessary to determine a diagnosis and etiology for PAP. Of note, care should be taken when performing WLL following a lung biopsy. Adequate time, at least 4–8 weeks, should elapse before performing a lavage which involves the biopsy site to allow adequate healing. There is an increased risk of hydrothorax from filling the freshly biopsied lung with fluid under pressure.

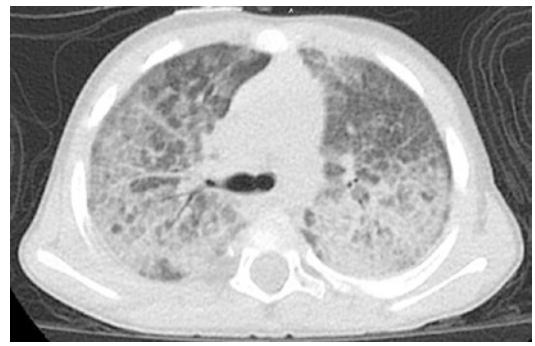

Fig. 38.2 Hereditary pulmonary alveolar proteinosis computed tomography of the chest demonstrating bilateral diffuse ground glass opacities with a reticular pattern of septal thickening: "crazy paving"

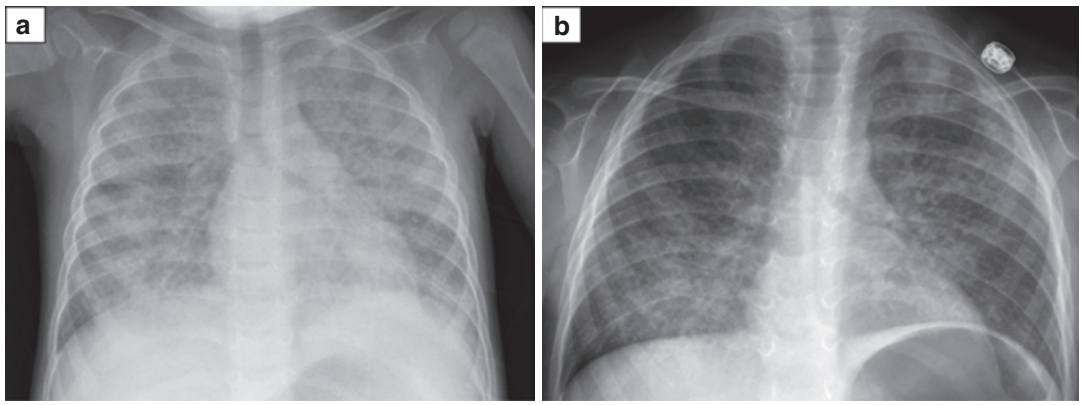

Fig. 38.1 Hereditary pulmonary alveolar proteinosis chest radiograph (**a**) before and (**b**) after segmental whole-lung lavage using a flexible bronchoscope

Fig. 38.3 Three- and one-liter suction canisters with bronchoalveolar lavage (BAL) fluid from a hereditary pulmonary alveolar proteinosis patient following segmental whole-lung lavage using a flexible bronchoscope demonstrating the turbid "potato soup" appearance of BAL containing proteinaceous material still in suspension (right) and the appearance after the protein sediments out if present in high amounts (left)

Determining the underlying etiology is important because not all patients with PAP benefit from WLL. The degree of therapeutic response depends not only on the effectiveness of protein clearance, but also on the underlying lung parenchyma. Patients with disruptions in GM-CSF signaling, either autoimmune or hereditary, frequently have limited disruptions in their alveolar architecture, although some develop fibrosis over time [10], and so many of them benefit significantly from WLL, at least in the early disease stages. However, patients with mutations in genes critical for surfactant protein production often have associated non-specific interstitial pneumonia in addition to PAP [5], and so their response to WLL is highly variable, patient specific, and may change over time. The anticipated response to WLL in secondary PAP is also very patient and disease specific.

Timing of Whole-Lung Lavage

The optimal time to perform an initial, or subsequent, WLL in a patient with PAP, or other condition, is unknown given the risks and frequently transient benefits of the procedure and varies among centers [11]. Determination of timing is made based on a combination of symptom severity and objective measures of oxygenation via blood gas measurements, six-minute walk test, overnight oximetry measurements, or a combination. The amount of time patients can go between lavages varies greatly from 4–6 weeks to 2–3 years or longer, even within families. The duration depends on the effectiveness of the lavage, underlying disease process, and other unknown patient-specific factors. Some centers advocate for earlier lavages more often because waiting until the patient is symptomatic and significantly hypoxic increases the risks associated with the procedure.

General Considerations

The basic concept of WLL is the same regardless of the technique utilized: fill and empty the lung with enough fluid to wash out the material while keeping the patient safe and comfortable. The procedure is usually performed under general anesthesia, frequently with muscle relaxation to prevent cough and dislodgement of the ventilation and/or lavaging tubes. While ECMO can be, and has been, utilized to facilitate WLL of both lungs simultaneously in patients felt to be too small or unstable for other approaches, there is risk for bleeding due to anti-coagulation and the ability to perform serial WLL's may be limited by vascular access. While performing WLL on the entirety of both lungs during a single anesthetic session has been reported [11], many centers lavage up to one lung at a time and return to the operating room at a later date, typi-

cally 3–7 days later, to lavage the contralateral lung.

Both lungs are frequently impacted similarly from PAP. The right lung, being slightly larger, may better tolerate single-lung ventilation when diseased, and so frequently the left lung is lavaged first. Even so, usually there are more significant desaturations during the first WLL compared to the second on the contralateral side. Two primary exceptions to this approach would be if the disease is unevenly distributed and felt to be more severe on the right suggesting the left lung would better tolerate single-lung ventilation or if a biopsy was recently performed on the left lung.

The accumulation of abnormal material in PAP is at the alveolar level; however, because of the anatomy and mechanics of the lung, fluid flow (air normally but saline during WLL) through the airways is by bulk flow and within the alveoli by Brownian motion because of the large relative cross-sectional area of the terminal bronchioles and alveoli compared to the trachea and central airways. Therefore, in order to facilitate mobilization of sediment into the fluid so it can then be removed, significant mixing needs to occur at the alveolar level where fluid flow is slowest. This can be achieved by applying external chest percussion during the procedure. The optimal frequency and intensity of percussion to agitate sediment into suspension within the fluid is unknown, but higher frequencies should theoretically be better at the alveolar level. This can be achieved by utilizing mechanical percussors set to near maximum frequency. Keeping two appropriate percussors available during procedures should be considered because of their tendency to overheat and shut off when used continuously for more than 1 hour.

During WLL, the patient frequently becomes mildly to moderately more hypoxic than baseline depending on the severity of the lung disease and the lavage technique. Hypoxia results from worsened ventilation-perfusion mismatching during single-lung ventilation and potential spill over from the lavage into the ventilated areas of the lung. During single-lung ventilation, oxygen saturations will frequently oscillate during the procedure reaching a nadir when the lavaged lung is empty of fluid and ventilation-perfusion mismatch greatest but improve as the lavaged lung fills with fluid under pressure, which once greater than capillary filling pressure shunts blood flow toward the ventilated lung. Otherwise normal patients should be able to tolerate mild-to-moderate hypoxia for the time it takes to complete a WLL as long as adequate perfusion is maintained. However, this can be a significant source of anxiety for the anesthesia team supporting the WLL (as well as the bronchoscopist) and needs to be discussed ahead of time including what degree of hypoxia will be tolerated versus what will indicate the procedure should be terminated.

Preparation

Normal saline is the most frequently utilized fluid for WLL [11]. The amount of fluid necessary to complete the procedure depends on the technique utilized and is individualized for each patient, but in general, adolescents and adults require 15–25 L of fluid per lung which is scaled down in younger children (roughly 200–400 mL/kg). Utilizing 3 L bags of normal saline is prudent because of the amount of fluid needed and to lessen the frequency of bag changes during the procedure. The day prior to the procedure, the bags to be used may be placed in a warmer, set at 37–40 °C, to minimize the large volume of fluid's impact on the patient's body temperature.

To facilitate the filling and emptying of the lung with fluid, and to minimize spilling fluid on the operating room floor, prior to the procedure, the Y-adapter from a double-lumen endotracheal tube and two bladder irrigation sets are utilized to create a closed circuit connecting the in-flow bag and its tubing to the out-flow bag and its tubing. A clamp placed across the tubing near the patient is alternated between the in-flow and out-flow lines to control the direction of fluid flow. The irrigation sets have in-line drip chambers which are useful for monitoring fluid flow and determining when flow has terminated, and the irrigation sets' ability to attach two bags at a time facilitates changes between bags. Once set up, a

bag of saline is hung and the tubing all the way to the drainage bag is primed with fluid before the procedure starts. The drainage bag is placed on the floor to facilitate flow by gravity.

Double-Lumen Endotracheal Tube Technique

The safest and seemingly most effective WLL techniques involve the isolation of the lavaged and ventilated lungs during the procedure. This is readily achieved with a double-lumen endotracheal tube. The smallest double-lumen endotracheal tube available is 26 Fr (approximately 8.3 mm outer diameter) and therefore can only be used in older children, adolescents, and adults. Using a left-sided double-lumen endotracheal tube, regardless of the side to be lavaged, allows for maximal ventilation when lavaging the left lung and maximal sediment clearance of the right upper lobe when lavaging the right. The left-sided tube is placed in the usual way with the bronchial tube in the left mainstem bronchus. Correct tube position is verified by flexible bronchoscopy through both lumens, starting with the tracheal lumen. Going through the tracheal lumen allows visualization of tracheal rings upon exiting the lumen along with the entirety of the right lung anatomy, to verify that the tube was not placed deep into a mainstem bronchus, frequently the right. The tracheal and bronchial endotracheal tube cuffs are inflated to produce a tight seal with their respective walls. Remember, the balloons are preventing fluid from spilling from the lavaged lung into the ventilating contralateral lung, so be extra certain they are functional and tight against the airway walls. A dose of corticosteroids may be given if there are concerns about airway wall injury and edema resulting from the high cuff pressures. Care should be taken to ensure the inflated bronchial cuff does not cross the carina and obstruct the right mainstem bronchus. Once the position is verified, the endotracheal tube should then be tightly secured.

The patient is then rotated into a decubitus position with the ventilated lung dependent. This position allows for the entire lavaged lung to be accessed during chest percussion, and it also provides a theoretical flow advantage for the draining fluid and sediment contained within the fluid. The patient is padded and supported appropriately. The endotracheal tube position is then reverified by passing the flexible bronchoscope through both lumens to ensure the tube did not shift during patient positioning.

Single-lung ventilation is then initiated in a pressure-regulated mode remembering that the anticipated tidal volume is roughly half of normal and so the respiratory rate will need to be increased. Once the patient is stable, the contralateral lung is filled with fluid by gravity. Keeping the bag of saline 30–40 cm above the level of the patient's lung controls the filling pressure. The initial filling of the lung is performed slowly, over about 10 minutes, to allow the resorption of the air trapped within the lung along with the normal physiologic surfactant. The fluid is allowed to drain into the patient until flow slows to a stop, and then the clamp across the drain line is removed and placed across the fill line. The fluid then drains from the patient into the empty bag on the floor. Once flow of the fluid draining from the patient has slowed to a stop, the clamp is switched back from the fill line to the drain line for the next cycle. The initial fill cycle is completed slowly, but the initial drainage and subsequent fill/drain cycles of the lung are allowed to proceed at the maximum rate allowed by the size of the tubing.

After the fluid flow is ensured and the patient stable, then chest percussion is initiated to the lung undergoing lavage. This greatly improves sediment mobilization and clearance within the fluid, which can be assessed comparing the turbidity of the fluid from the second drainage cycle to the fluid from the first cycle. During the subsequent drain and fill cycles, the patient should be closely monitored. Oscillation in the patient's oxygenation should be expected as the fluid fills and drains from the lung because of changes in ventilation-perfusion matching. However, sudden unexpected changes in ventilation, oxygenation, or hemodynamic parameters may suggest a complication has occurred such as a hydrothorax or deflated endotracheal tube cuff with leakage of

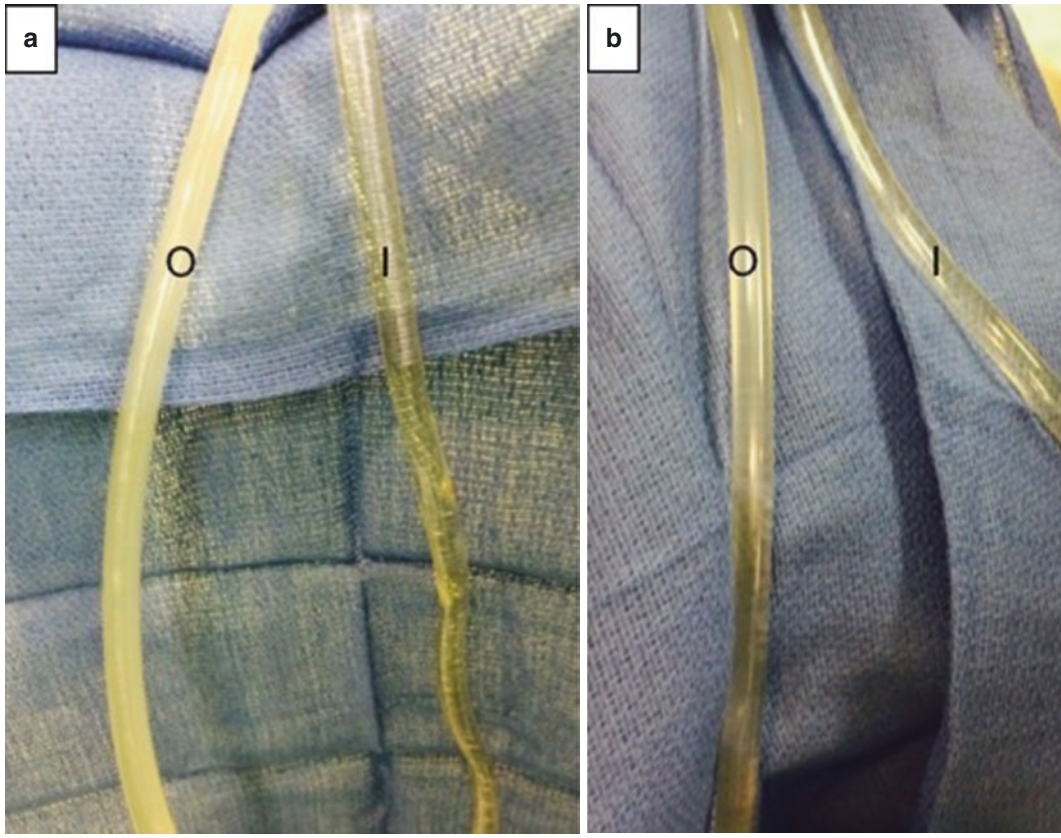

Fig. 38.4 Inflow (I) and outflow (O) lines carrying saline near the start (**a**) and conclusion (**b**) of a whole-lung lavage demonstrating the initial turbidity in the outflow line that clears during the procedure

fluid into the ventilating lung. If a complication is suspected, the lavaged lung should be drained immediately while assessing the cause of the change and determining if the procedure should continue or be aborted.

Filling and draining the lung with fluid while applying external percussion is continued until the return fluid is essentially clear (Fig. 38.4), suggesting maximal therapeutic benefit has been achieved, or the patient begins to not tolerate the procedure. Once it is decided to terminate the procedure, then percussion is stopped, and the lung allowed to completely drain. A suction catheter is passed into the endotracheal tube to suction out any residual fluid. The lavaged lung is then recruited utilizing manual bag ventilation and slow, sustained recruitment breaths at a pressure around 30 cm water. The endotracheal tube is then suctioned again followed by additional recruitment maneuvers before resuming double-lung ventilation. The patient is then turned over to anesthesia for emergence, extubation, and recovery. Because of the therapeutic benefit experienced by most patients, recovery is similar to a routine flexible bronchoscopy with BAL performed under general anesthesia. Stable outpatients may be able to go home the day of the procedure.

Alternative Techniques

Performing WLL in children too small to accommodate a double-lumen endotracheal tube poses unique challenges but is possible, and the general concept is the same: isolate and protect the ventilating lung from the areas of the lung being lavaged as much as possible. Utilizing two cuffed

endotracheal tubes placed side by side within the trachea seems an appealing approach, but there is considerable loss in cross-sectional area around the endotracheal tubes within the trachea that could be utilized for ventilation or lavage.

An effective technique most analogues to the double-lumen technique described previously involves first nasally intubating the patient with a cuffed endotracheal tube and, at first, leaving the tube in the trachea with the cuff deflated. A second endotracheal tube or alternatively a nasopharyngeal tube, which is to be used to ventilate the patient during the procedure, is then placed transnasally into position just above the larynx. Nasal intubations are utilized to increase the tube's stability during the procedure. Double-lung ventilation with the second laryngeal tube is then attempted to ensure that there is not too much obstruction caused by the first tracheal tube. If unsuccessful, then the tube sizes being used should be reconsidered. Once the patient is tolerating double-lung ventilation via the laryngeal tube adequately, the tracheal tube is then advanced under bronchoscopic guidance into the mainstem bronchus of the lung to be lavaged and the cuff inflated tightly. When the right lung is being lavaged, the right upper lobe is excluded and needs to be cleaned out utilizing a different technique, frequently a bronchoscope (see below). An orogastric tube is placed into the stomach to suction out air, which accumulates during ventilation using this technique. In order to prevent pressure leak and maximize ventilation, the mouth needs to be sealed with tape. When utilizing this set-up, the patient frequently remains in the supine position during the lavage to minimize the risk for tube displacement. The lung lavage then proceeds in the same manner as described for the double-lumen tube, utilizing percussion as able and tolerated. Small infants (3.6 kg) have been reported to be lavaged successfully via this technique.

If the patient is unable to tolerate this set-up, our next consideration would be to perform segmental lung lavages with a bronchoscope. This technique is nearly identical to performing a diagnostic bronchoalveolar lavage (BAL) utilizing wall suction. The bronchoscope is advanced distally into the segment being lavaged until a wedge is formed. Normal saline is instilled, typically 10–20 mL per aliquot depending on the size of the patient, and then suctioned out. Ideally, percussion is applied externally during the lavage at a location on the chest wall that results in visible vibration of the bronchoscope view. Lavage is repeated in the same segment until the return fluid is nearly clear before moving onto the next segment. This can take 10–20, or more, lavages per segment. Placing a loop within the suction tubing as it exits the bronchoscope to temporarily collect the effluent facilitates inspection of the fluid for sediment clearance. Although time and labor intensive, a whole lung can be effectively lavaged this way during a single session (Figs. 38.1 and 38.3). Frequently, multiple bronchoscopists and assistants are required to complete the procedure and attention needs to be paid to patient and bronchoscopist positioning to minimize the strains placed on both.

There are multiple ventilation strategies that can be utilized while using a bronchoscope for therapeutic WLL. If the patient can tolerate single-lung ventilation, then a cuffed endotracheal tube can be advanced transnasally, under bronchoscopic guidance, into the mainstem bronchus of the lung to be ventilated, and the cuff inflated to protect the lung from fluid spillover. The bronchoscope is then advanced through the opposite nare into the contralateral lung for lavage. In order to use this approach, the patient needs to be large enough to accommodate the ET tube and the bronchoscope within the larynx and trachea without causing undo trauma. Because the ventilated lung is fully protecting from spillover, this approach allows the patient to be placed in the decubitus position with the lavaged lung up, facilitating fluid return during lavage and application of external percussion. Therefore, while more labor intensive on the bronchoscopist, this approach may offer some advantages in sediment clearance over the previously described two endotracheal tube technique where the patient is frequently left supine during the procedure because of the more precarious nature of the tube positions.

If the patient is unable to tolerate single-lung ventilation, then the bronchoscope can be advanced either through, or alongside, a traditionally placed endotracheal tube within the trachea. Because there is no cuff protecting the non-lavaged areas of the lung being utilized for ventilation, the patient typically either remains supine or, alternatively, the patient is positioned in the lateral decubitus position with the lavaged lung dependent to minimize spill over into the contralateral lung. The primary benefit of this approach is that all of both lungs not being lavaged are available for ventilation. Therefore, this approach can be used on even the sickest patient and the amount of lung lavaged during any single session can be tailored based on the patient's tolerance of the procedure. If clearance of the lavaged areas of the lung is effective, then as the patient improves they should subsequently be able to tolerate more aggressive lavages until they are able to tolerate a single-lung ventilation technique.

Fluid Analysis

The fluid collected during a whole-lung lavage can be analyzed clinically in a manner similar to standard bronchial alveolar lavage (BAL) fluid, i.e., cell counts, cytology, culture, and PCR studies. However, the fluid can be cumbersome to handle given the 3 L bags utilized during the procedure, and the fluid dilution factor is different than typical BAL fluid. Therefore, if clinical fluid analysis is desired, a traditional BAL sample should be collected at the beginning of the procedure from the lung to be lavaged. Research laboratories perform other analyses on the whole lung lavage fluid, but that is beyond the scope of this paper.

Conclusion

WLL is a specialized therapeutic procedure that yields great benefits to patients when performed properly and safely. The indications for WLL are rare in pediatric patients, and therefore, the procedure is not frequently performed even at large pediatric referral centers. Pediatric pulmonologists should be familiar with the indications for and understand the basic concepts of performing the procedure.

Acknowledgments The authors would like to acknowledge the mentorship and guidance of Robert E. Wood, MD, PhD, who personally developed many of the techniques described and has taught them to countless pediatric pulmonologists (including C.T.T.). They would also like to acknowledge the dedication and tireless support of the bronchoscopy respiratory therapists, anesthesiologists, nurses, and operating room staff of Cincinnati Children's Hospital, without whom these procedures could not be performed.

References

1. Wong CA, Wilsher ML. Treatment of exogenous lipoid pneumonia by whole lung lavage. Aust NZ J Med. 1994;24(6):734–5.
2. Wilt JL, Banks DE, Weissman DN, Parker JE, Vallyathan V, Castranova V, et al. Reduction of lung dust burden in pneumoconiosis by whole-lung lavage. J Occup Environ Med. 1996;38(6):619–24.
3. Suzuki T, Trapnell BC. Pulmonary alveolar proteinosis syndrome. Clin Chest Med. 2016;37(3):431–40.
4. Suzuki T, Sakagami T, Young LR, Carey BC, Wood RE, Luisetti M, et al. Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. Am J Respir Crit Care Med. 2010;182(10):1292–304.
5. Griese M. Pulmonary alveolar proteinosis: a comprehensive clinical perspective. Pediatrics. 2017;140(2): e20170610
6. Liu Y, Chen LL, Qiu YY, Xiao YL, Cai HR. Clinical features of secondary pulmonary alveolar proteinosis associated with myelodysplastic syndrome: two case reports. Medicine (Baltimore). 2017;96(44):e8481.
7. Chauhan S, Sharma KP, Bisoi AK, Pangeni R, Madan K, Chauhan YS. Management of pulmonary alveolar proteinosis with whole lung lavage using extracorporeal membrane oxygenation support in a postrenal transplant patient with graft failure. Ann Card Anaesth. 2016;19(2):379–82.
8. Hisata S, Moriyama H, Tazawa R, Ohkouchi S, Ichinose M, Ebina M. Development of pulmonary alveolar proteinosis following exposure to dust after the Great East Japan earthquake. Respir Investig. 2013;51(4):212–6.
9. Chew R, Nigam S, Sivakumaran P. Alveolar proteinosis associated with aluminium dust inhalation. Occup Med (Lond). 2016;66(6):492–4.

10. Ono M, Saito R, Tominaga J, Okada Y, Ohkouchi S, Takemura T. Pathological features of explant lungs with fibrosis in autoimmune pulmonary alveolar proteinosis. Respirol Case Rep. 2017;5(5):e00255.

11. Campo I, Luisetti M, Griese M, Trapnell BC, Bonella F, Grutters J, et al. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. Orphanet J Rare Dis. 2016;11(1):115.

39 Treatment of Tracheobronchial Stenosis

Alvaro E. Pacheco

Flexible Bronchoscopy as a Diagnostic Tool in Tracheobronchial Stenosis

There are two main issues that flexible bronchoscopy addresses much better than rigid endoscopy when diagnosing a patient with airway stenosis: The first one is caused by the unreliability of rigid endoscopy to ascertain the presence of dynamic collapse of the tracheobronchial walls due to stenting of the airway by the telescope itself. The second one is caused by the impossibility of rigid bronchoscopes to explore the upper lobar bronchi due to their straight nature. Thus, the association of rigid and flexible bronchoscopy is probably the best situation for a thorough exploration of the stenotic airway. There are special situations, such as the complications of lung transplant patients, in which there is often a combination of stricture and malacia in the same anatomic region, making a combined exploration fundamental for the correct planning of the treatment in this patients [1–4].

Bronchography is another diagnostic tool that has been resurfacing in the last few years after being almost completely abandoned. It is extremely useful in outlining the airway in congenital tracheobronchial stenosis, in which there may be a significant number of different configurations, all of which require different surgical approaches. The use of high-resolution TC has been the gold standard to address this issue, but some authors use bronchography at the moment of the endoscopic evaluation during the workup of every tracheal stenosis patient. The presence of a stenotic bronchus often does not allow even the smallest flexible scope to go through not risking edema and further stricture, making impossible to explore the distal airway. Flexible scope-guided bronchography is a useful tool to discern from a stenotic vs an absent lumen, and also allows for a dynamic evaluation of the airway distal to the stenosis, in which there is often an associated malacic segment [5–7].

Bronchography also allows for a very accurate evaluation of the severely malacic airway, since it shows exactly the length of the airway that is compromised, making the stenting more accurate and successful. The use of the aspiration or working channel of the bronchoscope to inject diluted (1:1 with normal saline) iso-osmolar contrast allows obtaining excellent images of the bronchial tree, making bronchography a very good TC complement. In addition, some of the contrast can be suctioned back at the end of the procedure, thus decreasing the risk of atelectasis and chemical pneumonitis (Fig. 39.1).

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*,
Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_39

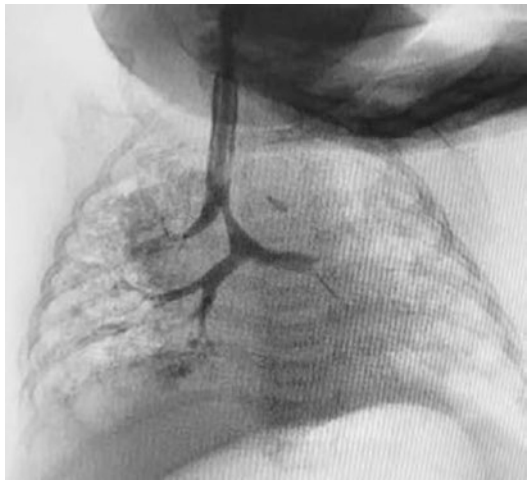

Fig. 39.1 Bronchography showing a congenital tracheal stenosis

Flexible Bronchoscopy as a Therapeutic Tool for Tracheobronchial Stenosis

The first critical issue is the careful selection of patients. As a general concept, tracheobronchial stenosis requiring surgical treatment refers to the symptomatic luminal obstruction of more than 50% in the trachea, main stem bronchi, bronchus intermedius, or lobar bronchus. The bronchoscopist has to weigh very carefully the benefits vs the risks of treating the distal airway, since the functional gain may not outweigh the risks involved in operating a thinner-walled airway, with higher chance of wall rupture during the procedure.

Relative contraindications are: lesions longer than 4 cm, present for 1 month or more, and oxygen requirements of more than 40% during hot ablative therapies (laser, electrocautery).

The next fundamental point is the choice of the correct bronchoscope. The instruments available for pediatric bronchoscopy vary in length and diameter of the bronchoscope itself, and in the diameter of the working channel. Table 39.1 shows examples of the various types of flexible bronchoscopes commonly used. As a general rule, if the bronchoscope is to be used through an endotracheal tube, the recommended diameter is at least 1 mm less than the inner diameter of the tube, so that the scope can move freely, avoiding jamming or damaging the instrument. The choice of the bronchoscope is also very important when another instrument is to be passed through its working channel (forceps, laser probe, electrocautery probe). The endoscopist should make sure the instrument passes freely through the channel and is long enough to go through the whole length of the endoscope [8–11].

Table 39.1 Pediatric flexible bronchoscopes

Maximum diameter	Working channel diameter
2.2 mm	None
2.8 mm	1.2 mm
3.5 mm	1.2 mm
3.6 mm	1.2 mm
4.9 mm	2.2 mm
5.0 mm	2.2 mm
3.8 mm (video)	1.2 mm
4.9 mm (video)	2.0 mm
5.3 mm (video)	2.0 mm
6.0 mm (video)	2.8 mm

The most frequent procedures used to treat a stenotic airway with a flexible bronchoscope are: laser dilatation, balloon dilatation, electrocauterization, and cryotherapy.

Laser Dilatation

The use of laser in the treatment of glottic or subglottic stenotic lesions is well known and documented, and routinely performed in many centers across the globe. There are some issues to take into account when using laser through a flexible bronchoscope. The first one is the type of laser to be used. Currently, there are several types of laser used in interventional bronchoscopy:

- The CO_2 laser is most frequently used in the larynx, because it is transmitted by a mirror system through the air, and targeted onto a red light spot, which is easy to aim with an operating microscope through a suspension laryngoscopy. Flexible CO_2 laser probes are now available that fit through any bronchoscope with a 1.2 mm working channel.

- The KTP (kalium-titanium-phosphate) laser is transmitted by means of a fiber, and when delivered at a low power range (<5 W), it can produce similar tissue effects as those seen with the CO_2 laser. Very thin fibers (0.6 mm) are available and can be used with any flexible bronchoscope with a working channel.
- The diode laser is similar to the KTP laser in its effect and probe size.
- The Nd:YAG laser has a significant in-depth effect, making it less suitable for its use in the pediatric population, especially in infants and young children. It is popular in adult practice, so it could be used in older children. It is delivered through a 1.6 mm probe that fits any bronchoscope with a 2 mm working channel [12–15].

The second issue to observe are the safety measures the endoscopist has to take to avoid external and endoluminal fire. The patient should be draped with moist towels and eye pads to minimize fires on the external body. To minimize risk of fire in the airway, the FiO_2 should be reduced to 21%, and confirmation from the anesthesiologist that inspiratory and expiratory concentrations are below 30% should be obtained before laser use.

The lesions most susceptible to laser treatment are membrane-like circumferential lesions with no compromise of the cartilaginous support of the airway. Laser is usually used as an adjunctive therapy to balloon dilatation of these lesions. 3–5 radiated incisions should be made to the membrane, always leaving intact mucosa between them. This allows for a more controlled radial dilatation with a balloon.

Complications are not frequent (usually present in fewer than 5% of the cases), and include bleeding, pneumothorax, pneumomediastinum, and death. The risk of perforation can be minimized by aiming the beam always parallel to the airway. The mortality has been attributed to air embolism as a result of high flow of air coolant and contact probes. It is recommended to use non-contact mode whenever possible while keeping the coaxial coolant air flow at a minimum level [13, 16, 17].

Balloon Dilatation

Balloon dilatation is a simple, rapid, and safe method to dilate a tracheal or bronchial stenosis. Originally described under fluoroscopic guidance, it is now performed under rigid or flexible bronchoscopic visualization most of the time. The procedure provides immediate improvement in the stenosis in almost all cases and offers excellent short-term relief. Long-term efficacy is dependent upon the pathophysiology of the underlying disease, the location and extent of the stenosis, and the use of adjunctive treatments (such as laser and electrocautery).

Before performing balloon dilatation, it is critical to carefully examine the airway to determine the length of the stenotic segment, the patency of the airway distal to the stenosis, and its proximity to airway branch points and vascular structures.

The equipment includes a balloon catheter, a guide wire, and a high pressure insufflation device with a manometer (Fig. 39.2).

There are balloons specifically designed for use in the airway, which are compatible with a 2.8 mm working channel bronchoscope. (Bryan Medical, Boston Scientific). The use of balloons designed for cardiac catheterization interventions can be adopted for this procedure with many able to be used in a 2.0 mm working channel.

In neonates, infants, and small children, the balloon has to be inserted alongside the endoscope

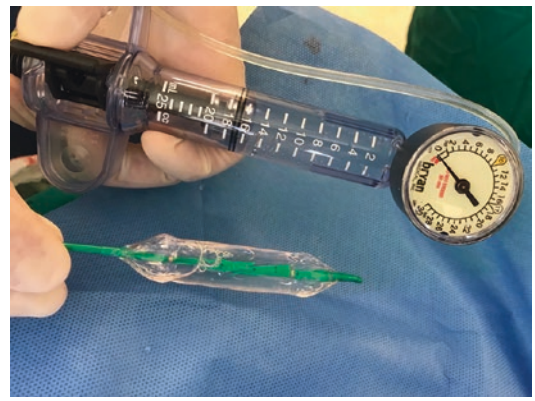

Fig. 39.2 Balloon specifically designed for its use in the airway. (Manufactured by Bryan Medical Inc. Cincinnati, OH)

until it reaches the stenotic segment. Fluoroscopic guidance can also be used, since balloon catheters have proximal and distal radiopaque markers.

The choice of the appropriate size both in length and inflatable diameter of the balloon is critical, as too long or wide a balloon can result in distal airway trauma. It should be based on the size of the normal airway lumen proximal to the area of obstruction. In the case of a stenosis of the right or left main bronchus close to the carina, the diameter of the contralateral bronchus is used to determine the size of the balloon to be used.

The balloon should be positioned across the area to be dilated, and the proximal end of the balloon should be positioned approximately 0.5 cm proximal to the stricture. The balloon is then inflated using sterile water to its desired pressure. Inflation times vary from 30 to 120 seconds, depending on the patient's tolerance. In general, a graded and incremental dilatation with repeated inflation/deflation cycles progressing to desired luminal diameter is recommended.

The balloon must be completely deflated before withdrawing, and care should be taken not to pull the catheter while inflated, because it may damage the drainage channel, making it impossible to deflate. In this case, the balloon should be ruptured with a sharp instrument immediately to allow its removal.

Bronchoscopy is then repeated to evaluate the result, to determine the need for further dilatation, and to evaluate for complications.

Complications are infrequent. Hebra et al. reported a 15-year experience of 158 procedures done in 37 children. They noted mild complications in 7% of the procedures. Even so, one must be aware of potential damage to the mucosa (superficial or deep), transmural tears, bleeding, pneumomediastinum, and pneumothorax. Most of the time this complications are self-limited and require only conservative treatment and close observation [18–23].

Electrosurgery

Electrosugery has been used safely and successfully since the early 80s in the treatment of tracheobronchial stenosis as a "poor man's alternative" to laser. There are two main electrosurgical modalities currently used in the clinical setting: electrocautery and argon plasma coagulation (APC).

Electrocautery

Electrocautery (EC) is a contact form of electrosurgery, where high-frequency alternating current is conducted from the probe to the tissue through air, causing tissue coagulation, hemostasis, carbonization, and vaporization, depending on the power used, the tissue, the application time, and the contact surface area. In airway use, only coagulation and hemostasis are used, since the other modes generate local complications (granulation tissue, scarring, and restenosis). Table 39.2 summarizes the thermal effects of EC in biological tissue. Electrocautery instruments commonly used with bronchoscopy include round probe, knife, wire snare, and forceps (Fig. 39.3).

These instruments fit through a 2 mm working channel. Care must be taken to always use an insulated bronchoscope to avoid an electroshock to the endoscopist while applying the electrical current.

Like in laser surgery, it is necessary to limit the inspired oxygen concentration, and confirm inspiratory and expiratory concentrations below 30% with the anesthesiologist to avoid airway fires.

Most modern electrosurgery units allow for combined cut/coag modes, making it possible to have a clean, almost bloodless surgical field.

Table 39.2 Thermal effects on biological Tissue

Temperature	Effect
37–40 °C	None
>40 °C	Hyperthermia, depending on the duration of the exposure, the tissue can recover or die
>60 °C	Devitalization due to denaturation and shrinkage of connective tissue
>100 °C	Vaporization of tissue fluid, which leads to cutting due to mechanical tearing of the tissue
>150 °C	Carbonization
>300 °C	Vaporization

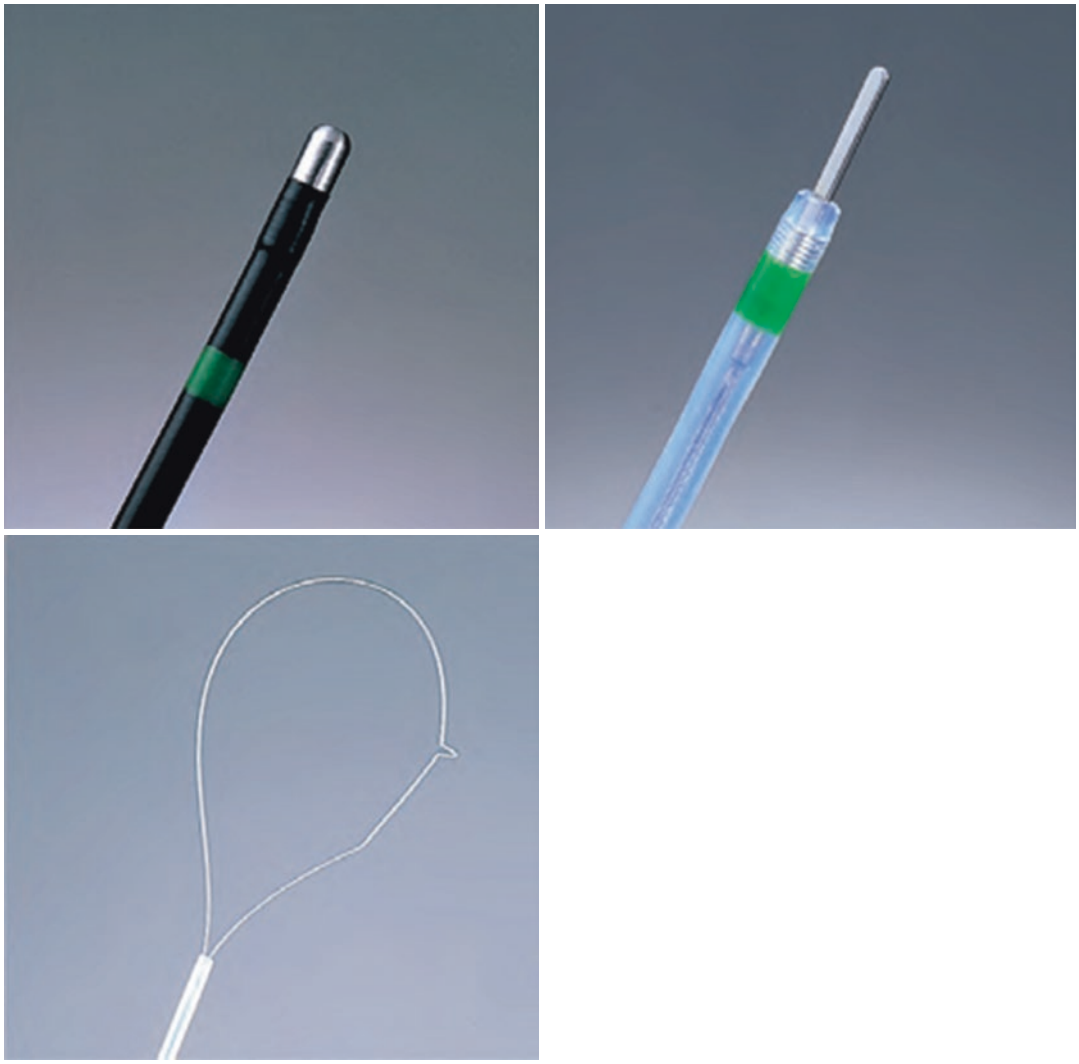

Fig. 39.3 From left to right: Round coagulation probe, electrosurgery knife, wire snare. (Manufactured by OLYMPUS AMERICA, Mellville, NY)

In the treatment of tracheobronchial stenosis, the electrocautery knife is the preferred instrument, because it allows for precise cutting of the scar tissue. As with the laser, it is usually a two-step approach: making radial incisions leaving intact mucosa in between, and balloon dilatation of the stenotic segment.

The most common complication is minor bleeding, although airway fires and airway perforation are possible. To limit the damage to the airway walls, the power should be limited to ≤40 W, and the application time to ≤2 sec [24–27].

Argon Plasma Coagulation (APC)

APC has been available in endoscopic surgery since the early 90s. It uses an ionized argon gas jet flow (plasma) to conduct electrons allowing a noncontact mode of treatment (lightning effect). Heat energy produced by this process causes the tissue coagulation or hemostasis. The heat evaporates tissue water and denaturates protein, producing the coagulative and destructive effects. It does not result in tissue carbonization. The depth and tissue volume affected depend on the voltage applied to the gas and the application time. At the

usual settings (<50 W for ≤2 sec), the depth of penetration is <5 mm.

Currently, there are flexible probes that range from 1.5 to 2.3 mm, which can be passed through a bronchoscope's working channel.

As with all hot ablative instruments, care should be taken to reduce the inspiratory/expiratory concentration of oxygen in the patient's airway prior to applying current inside the airway.

The probe tip should be extended at least 1 cm beyond the tip of the bronchoscope, to avoid damaging the instrument. The usual gas flow rate is between 0.3 and 0.8 L/min. The probe should be placed within 1 cm of the target, but not in contact with it, to allow the gas to flow. Short bursts (2–3 sec) of current are applied. The resulting debris can be removed with forceps.

Since the treated area is not as precise as the one obtained with an electrocautery knife, APC is not as useful in tracheobronchial web-like stenosis, but there are reports of good results in thicker and more severe lesions, and specially in the removal of granulation tissue thanks to its excellent hemostatic properties. It is also very useful for in-stent overgrowth of obstructing granulation tissue.

Complications are infrequent, but cardiopulmonary arrest and cerebral gas embolism have been reported due to a higher gas flow rate (greater than 1–2 L/min). Airway perforation has also been reported at a very low rate (1.4% in a large series). The risk of perforation is diminished by using low voltage (10–30 W) and short exposure times (2–3 sec) [28–33].

Cryotherapy

Cryotherapy is the use of extreme cold to destroy tissue using rapid freeze-thaw cycles. It has been used with flexible bronchoscopes since the advent of a flexible cryoprobe in 1994. When tissue is exposed to extreme cold, cell death is induced by various mechanisms that include direct damage by the formation of ice crystals, and delayed damage through vascular and immunologic phenomena. Tissue cryosensivity depends on its water content and vascularity. Cartilage, connective tissue, fat, and fibrosis are known to be cryoresistant, whereas granulation tissue, skin, and mucous membranes are cryosensitive.

There are two main modalities for the use of bronchoscopic cryotherapy: cryoprobe-based therapy, in which tissue damage occurs when the cryoprobe is brought into contact with the target tissue, and spray cryotherapy, in which liquid nitrogen is applied directly onto the target tissue, causing flash freezing.

Flexible cryoprobes are available in 1.9 and 2.4 mm (Erbe USA Inc., Marietta, GA). In spray cryotherapy liquid nitrogen is sprayed through a 2.4 mm catheter that is inserted through the working channel of the bronchoscope.

Cryotherapy was originally used in the treatment of tracheobronchial malignancies, but there are several reports of benign central airway obstruction treated with cryotherapy successfully, sometimes as an adjunctive therapy, and sometimes as a standalone therapy [34–37].

Probe Cryotherapy

The probe should be advanced 1 cm beyond the tip of the bronchoscope, and put in contact with the target tissue. It is then activated for 30 seconds by a foot pedal. This allows for freezing of the tissue. The thawing cycle begins passively by the deactivation of the pedal. This cycle is usually repeated 2–3 times before moving on to an adjacent tissue. The area of tissue injury is estimated in roughly 1 cm in diameter and 3 mm in depth. It is noteworthy that cryotherapy usually has a delayed effect, and that devitalized tissue must be removed during the first week after the initial treatment. In fact, initial edema and necrotic tissue may cause further narrowing of the airway, making cryotherapy a poor choice in critical or emergent airway obstruction [38, 39].

Spray Cryotherapy

There are many safety issues regarding the use of spray cryotherapy in the airway. Liquid nitrogen is a rapidly expanding cryogen that can cause barotrauma from high intrathoracic pressures, as well as hypoxemia as nitrogen displaces inspired oxygen. It is imperative to take precautions that allow the escape of the rapidly expanding liquid

nitrogen during spray cryotherapy (deflating the ET tube cuff, disconnecting ET tube bronchoscope adapters, holding ventilation during spray delivery, using an airway large enough to allow the egress of the gas).

In 2012, the advanced truFreeze device (CSA Medical, Inc. Lexington, MA) was approved by the US FDA for cryogenic destruction of tissue using liquid nitrogen spray requiring either active or passive ventilation during surgical procedures.

The procedure is usually done under general anesthesia with an ET tube. The spray is applied in intervals of 5 seconds, timed from onset of visible mucosal frost formation reaching 50% of the target area. Complete thawing of at least 30 seconds is allowed between each application.

As with probe cryotherapy, a treatment delay can be expected and initial edema ant tissue necrosis can further obstruct the airway. It is not the treatment of choice for critical or emergent airway obstruction either [40, 41].

Bibliography

1. Soyer T. The role bronchoscopy in the diagnosis of airway disease in children. J Thorac Dis. 2016;8(11):3420–6.
2. Wood RE, Fink RJ, Wood E. Applications of flexible Fiberoptic bronchoscopes in infants and children. Chest. 1978;73(5):737–40.
3. Carden KA, Boiselle PM, Waltz DA, Ernst A. Tracheomalacia and tracheobronchomalacia in children and adults: an in-depth review. Chest. 2005;127(3):984–1005.
4. Kendig, Edwin L., Robert W. Wilmott, and Victor Chernick. Kendig and Chernick's disorders of the respiratory tract in children. Elsevier Health Sciences, 2012. p. 131–44.
5. Bramson RT, Sherman JM, Blickman JG. Pediatric bronchography performed through the flexible bronchoscope. Eur J Radiol. 1993;16(2):158–61.
6. Speggiorin S, Torre M, Roebuck DJ, McLaren CA, Elliott MJ. A new morphologic classification of congenital tracheobronchial stenosis. Ann Thorac Surg. 2012;93(3):958–61.
7. Jenkins P, Dick R, Clarke SW. Selective Bronchography using the Fiberoptic bronchoscope. Br J Dis Chest. 1982;76:88–90.
8. Gilbert CR, Wang K, Lee HJ. Interventional pulmonology in the pediatric population. Semin Respir Crit Care Med. 2014;35(6):751–62.
9. Midulla F, de Blic J, Barbato A, Bush A, Eber E, Kotecha S, et al. Flexible endoscopy of paediatric airways. Eur Respir J. 2003;22(4):698–708.
10. Perez-Frias J, Moreno Galdó A, Perez Ruiz E, Barrio Gomez De Aguero MI, Escribano Montaner A, Caro Aguilera P. Normativa de broncoscopia pediátrica. Arch Bronconeumol. 2011;47(7):350–60.
11. Singh V, Singhal KK. The tools of the trade — uses of flexible bronchoscopy. Indian J Pediatr. 2015;82(10):932–7.
12. Dutau H, Breen DP. Endobronchial laser treatment: an essential tool in therapeutic bronchoscopy. Interv Pulmonol. 2010;June:149–60.
13. Lee GS, Irace A, Rahbar R. The efficacy and safety of the flexible fiber CO2 laser delivery system in the endoscopic management of pediatric airway problems: our long term experience. Int J Pediatr Otorhinolaryngol. 2017;97:218–22.
14. Ward RF. Treatment of tracheal and endobronchial lesions with the potassium titanyl phosphate laser. Ann Otol Rhinol Laryngol. 1992;101(3):205–8.
15. Mohan A, Guleria R, Mohan C, Sharma R. Laser bronchoscopy-current status. J Associat Phys India. 2004;52:915–20.
16. Sachdeva A, Pickering EM, Lee HJ. From electrocautery, balloon dilatation, neodymium-doped:yttrium-aluminum-garnet (Nd:YAG) laser to argon plasma coagulation and cryotherapy. J Thorac Dis. 2015;7(Suppl 4):S363–79.
17. Remz M, Luria I, Gravenstein M, Rice SD, Morey TE, Gravenstein N, et al. Prevention of airway fires: do not overlook the expired oxygen concentration. Anesth Analg. 2013;117(5):1172–6.
18. Cohen MD, Weber TR, Rao CC. Balloon dilatation of tracheal and bronchial stenosis. Am J Roentgenol. 1984;142(3):477–8.
19. Hebra A, Powell DD, Smith CD, Biemann Othersen H. Balloon tracheoplasty in children: results of a 15-year experience. J Pediatr Surg. 1991;26(8):957–61.
20. McArdle JR, Gildea TR, Mehta AC. Balloon Bronchoplasty: its indications, benefits, and complications. J Bronchol Interv Pulmonol. 2005;12(2):123–7.
21. Shitrit D, Kuchuk M, Zismanov V, Rahman NA, Amital A, Kramer MR. Bronchoscopic balloon dilatation of tracheobronchial stenosis: long-term follow-up. Eur J Cardio-thoracic Surg. 2010;38(2):198–202.
22. De Gracia J, Culebras M, Álvarez A, Catalán E, De la Rosa D, Maestre J, et al. Bronchoscopic balloon dilatation in the management of bronchial stenosis following lung transplantation. Respir Med. 2007;101(1):27–33.
23. Soong W-J, Tsao P-C, Lee Y-S, Yang C-F. Therapeutic flexible airway endoscopy of small children in a tertiary referral center—11 years' experience. Papadelis C, editor. PLoS One. 2017;12(8) online journal
24. Mahmood K, Wahidi MM. Ablative therapies for central airway obstruction. Semin Respir Crit Care Med. 2014;35(6):681–92.

25. Sutedja G, Van Kralingen K, Schramel FMNH, Postmus PE. Fibreoptic bronchoscopic electrosurgery under local anaesthesia for rapid palliation in patients with central airway malignancies: a preliminary report. Thorax. 1994;49(12):1243–6.
26. Amat B, Esselmann A, Reichle G, Rohde HJ, Westhoff M, Freitag L. The electrosurgical knife in an optimized intermittent cutting mode for the endoscopic treatment of benign web-like tracheobronchial stenosis. Arch Bronconeumol. 2012;48(1):14–21.
27. Bilaçeroğlu S. Endobronchial ablative therapies. Clin Chest Med. 2018;39(1):139–48.
28. Yasuo M, Tanabe T, Tsushima K, Nakamura M, Kanda S, Komatsu Y, et al. Endobronchial argon plasma coagulation for the management of post-intubation tracheal stenosis. Respirology. 2006;11(5):659–62.
29. Riechle G, Freitag L, Kullmann H, Prenzel R, Macha H, Farin G. Argon plasma coagulation in Bronchology: a new method – alternative or complementary? J Bronchol. 2000;7:109–17.
30. Zawadzka-Głos L, Chmielik M, Gabryszewska A. Treatment of postintubation laryngeal stenosis using argon plasma coagulation. New Med. 2003;6(2):2–3.
31. Sheski FD, Mathur PN. Endobronchial Electrosurgery argon plasma coagulation and electrocautery. Semin Respir Crit Care Med. 2004;25(4):367–74.
32. Reddy C, Majid A, Michaud G, Feller-Kopman D, Eberhardt R, Herth F, et al. Gas embolism following bronchoscopic argon plasma coagulation: a case series. Chest. 2008;134(5):1066–9.
33. Azizkhan RG, Lacey SR, Wood RE. Acquired symptomatic bronchial stenosis in infants: successful management using an argon laser. J Pediatr Surg. 1990;25(1):19–24.
34. Ni C, Yu H, Han X, Meng C, Zhang Y. Clinical analysis of bronchoscopic cryotherapy in 156 cases of pediatric patients. Int J Clin Exp Med. 2016;1(59):62–7.
35. Mathur PN, Wolf KM, Busk MF, Briete WM, Datzman M. Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. Chest. 1996;110(3):718–23.
36. DiBardino DM, Lanfranco AR, Haas AR. Bronchoscopic cryotherapy: clinical applications of the cryoprobe, cryospray, and cryoadhesion. Ann Am Thorac Soc. 2016;13(8):1405–15.
37. Jung Y-R, Taek Jeong J, Kyu Lee M, Kim S-H, Joong Yong S, Jeong Lee S, et al. Recurred post-intubation tracheal stenosis treated with Bronchoscopic cryotherapy. Intern Med. 2016;55(22):3331–5.
38. Marasso A, Gallo E, Massaglia GM, Onoscuri M, Bernardi V. Cryosurgery in bronchoscopic treatment of tracheobronchial stenosis; indications, limits, personal experience. Chest. 1993;103(2):472–4.
39. Schumann C, Hetzel M, Babiak AJ, Hetzel J, Merk T, Wibmer T, et al. Endobronchial tumor debulking with a flexible cryoprobe for immediate treatment of malignant stenosis. J Thorac Cardiovasc Surg. 2010;139(4):997–1000.
40. Bhora FY, Ayub A, Forleiter CM, Huang CY, Alshehri K, Rehmani S, et al. Treatment of benign tracheal stenosis using endoluminal spray cryotherapy. JAMA Otolaryngol Head Neck Surg. 2016;142(11):1082–7.
41. Janke KJ, El-Sayed Abbas A, Ambur V, Yu D. The application of liquid nitrogen spray cryotherapy in treatment of bronchial stenosis. Innov Technol Tech Cardiothorac Vasc Surg. 2016;11(5):349–54.

Excision of Airway Lesions

40

Christoph Hutchinson and David DiBardino

Epidemiology of Pediatric Endobronchial Lesions

Primary airway lesions in children are uncommon. The etiologies and behavior of endotracheal and endobronchial lesions are varied, and can be either benign or malignant [1, 2]. Tumors in the airway and lung of the pediatric population have an incidence reportedly as low as 0.2% [3]. In 2009, Neville et al. reviewed the Surveillance, Epidemiology, and End Results Program (SEER) database and reported an incidence of 0.049/100,000 [4]. Neoplastic tumors with malignant potential include pleuropulmonary blastoma, bronchial adenomas, carcinoid tumors, mucoepidermoid carcinomas, and adenoid cystic carcinomas. Benign tumors include hamartomas, subglottic hemangiomas, recurrent respiratory papillomatosis, inflammatory pseudotumors, leiomyomas, cysts, and mucus gland tumors [1, 2, 4–6]. Unlike in adults, most primary neoplasms of the trachea and larger airways in pediatric patients are benign [1]. Malignant neoplasms tend to be located in the more distal airways [1, 7]. Other less common airway lesions are infectious, (tuberculous or fungal) or iatrogenic. Iatrogenic causes of airway lesions include suprastomal granulation tissue in patients with tracheostomy, or granuloma formation from airway stents.

General Considerations: Airway Management and Endoscopic Equipment

Airway lesion management ranges from pure endoscopic resection to open surgical techniques. All ablative tools available to the interventional pulmonologist are delivered via the flexible or rigid bronchoscope. We recommend general anesthesia with an artificial airway for all procedures aimed at relieving airway obstruction given the potential for bleeding. Having complete control over the child's airway is essential [8].

The rigid bronchoscope, also known as an open tube bronchoscope, uses exchangeable barrels and can vary in diameter from 2 to 14 mm, and allows multiple instruments to be passed simultaneously into the airway. The rigid bronchoscope barrel acts as a conduit for instruments

Electronic Supplementary Material: The online version of this chapter (https://doi.org/10.1007/978-3-030-54924-4_40) contains supplementary material, which is available to authorized users.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_40

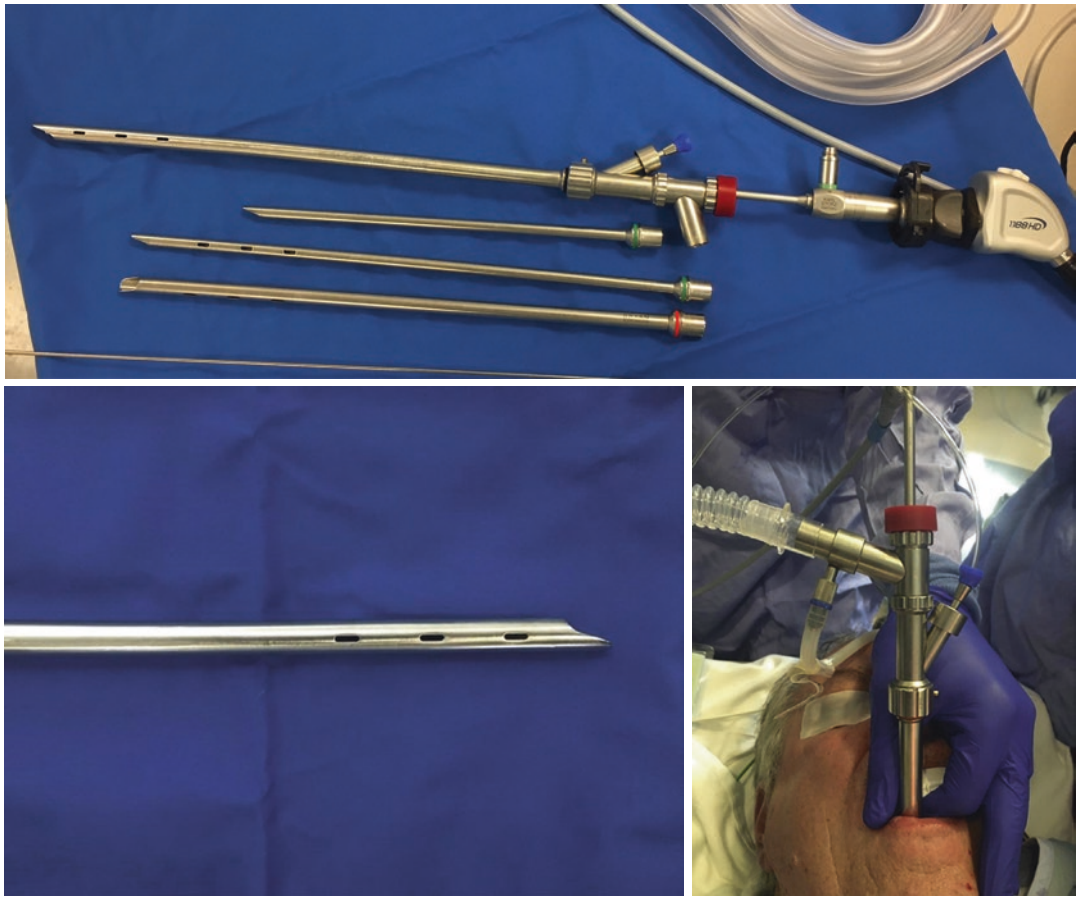

Fig. 40.1 12-mm diameter rigid bronchoscope with side ventilation ports (left & top). Rigid intubation allowing the use of a large bore suction catheter (right). Varying diameter and length interchangeable barrels (top)

while simultaneously acting as the airway. That allows for the passing of larger instruments directly via the rigid barrel while providing a large working channel for therapeutic interventions in both benign and malignant disease (Fig. 40.1). The rigid bronchoscope allows for maximal patient safety and control of the airway. It should be performed under general anesthesia, ideally using total intravenous anesthesia, paralysis, and jet ventilation [8–10].

Instrumentation via the flexible bronchoscope is limited by the size of the working channel. The flexible bronchoscope chosen must pass through an artificial airway and allow a large enough working channel to accommodate the ablation equipment desired. Bronchoscope diameters and working channel sizes vary by manufacturer. The Olympus BF-P190 bronchoscope™, a larger scope commonly used in pediatric interventions, has an outer diameter of 4.2 mm and a 2.0 mm working channel (Fig. 40.2). With this size bronchoscope, our common practice is to use either a 6.0 mm endotracheal tube or the smallest adult-sized laryngeal mask airways (LMA).

In children, the size of either rigid or flexible bronchoscope can be limited by the size of the airway; particularly in younger children and infants. Having training and access to both sets of instruments allows the interventionalist to select the most appropriate technique and instrument for a given clinical indication. Younger patients, with smaller airways, may present a unique challenge; particularly those under 10 years of age. In adults, the glottic opening is the narrowest part of the airway. In these younger children however, the cricoid cartilage represents the airway's smallest

Fig. 40.2 BF-P190 bronchoscope with 2.0 mm working channel

diameter. This anatomic limitation becomes important because an instrument that is able to be passed via the glottic opening may not pass distal to the cricoid [11]. The size of endotracheal appliances (rigid bronchoscope or endotracheal tube) is limited and affects the ability to utilize certain instruments. An LMA has the advantage of allowing full airway access, but the disadvantage of not providing a perfectly closed airway system for ventilation. Ventilation is often an issue when airway resistance is increased by airway bleeding and the bronchoscope itself occupying a large percentage of the airway [8]. If a flexible bronchoscope is desired, a child could undergo suspension laryngoscopy with jet ventilation to allow full access to the airway without being limited by the size of an artificial airway device [12].

Airway lesions in the pediatric population often requires a multidisciplinary team approach between otolaryngologists, pediatric surgeons, anesthesiologists, and pulmonologists. The role of the interventional pulmonologist is evolving in pediatric bronchoscopy as technology advances [10, 13]. The interventional bronchoscopist has an armamentarium of tools and techniques that may be used to intervene upon the various airway lesions encountered in the pediatric population. Generally, endobronchial lesions are managed endoscopically by physical tumor excision methods such as rigid barrel tumor core-out, microdebrider therapy, and cryorecanalization; or the use of ablative techniques such as laser ablation, probe cryotherapy, and argon plasma coagulation (APC). Turning to the literature for guidance, one finds endobronchial tumor ablation has been reported in case series and case reports in the pediatric population. When choosing an ablation modality on an airway lesion in the pediatric

population, it is important to remember that infants and younger children may have a soft and thin airway wall which is in very close proximity to large vascular structures [13]. As such, tools that are suited for the adult population may not be ideal for pediatrics.

Laser Therapy

LASER stands for light amplification by stimulated emission of radiation. Lasers can induce tissue vaporization, coagulation, homeostasis, and necrosis through a focused beam of monochromatic light. The biologic absorption of the laser depends on the wavelength emitted by the light source. The name of the laser refers to the type of material (solid, liquid, gas) used within the optical cavity as the laser medium. The laser medium determines the wavelength of the emitted radiation. Three lasers which are commonly employed in the airway in both adults and children are the carbon dioxide (CO_2), potassium-titanyl-phosphate (KTP), and neodymium:yttrium-aluminum-garnet (Nd:YAG) lasers. Other lasers less commonly employed in pediatrics are argon, krypton, and the helium-neon laser [14–16]. Laser ablation is mediated by the vaporization of extracellular and intracellular water attained at 100 °C and is followed by carbonization of the residual tissue.

The YAG laser has a wavelength of 1.06 m, low absorption, and relatively deep penetration with high scatter. The range for penetration depth varies in the literature based on tissue characteristics, the tissue pigment, and the distance from laser probe to the target surface. A range of 2–6 mm is generally accepted depending on all variables aforementioned [14, 17]. It is popular in the adult population for airway tumor resection and debulking. Due to its deeper penetration, it may be less well suited to the pediatric population.

The KTP laser has medium absorption and scatter with shallow penetration, and 0.5 m wavelength. Tissue penetration is more shallow than the YAG laser, with a depth of 0.5–2 mm [17]. When used at lower power settings, it is a good option for the pediatric population as it may be deployed via flexible or rigid and does not have as deep or as wide a field effect as the YAG laser.

Finally, the CO_2 laser has a 10.6 m wavelength, a high absorption with low scatter, and shallow surface vaporization. The depth of penetration is extremely limited with the vast majority of the energy being absorbed within 0.03 mm of depth [17]. It possesses a high water-absorption coefficient (250 cm^{-1}) that makes it readily absorbed by intracellular water. Unlike the YAG and KTP lasers which are deployed via a flexible fiber, earlier versions of the CO_2 laser could not be employed via a flexible bronchoscope, and required suspension laryngoscopy or rigid bronchoscopy. It was frequently used in the upper airway and larynx because it is air transmitted and relatively straightforward to aim under laryngeal suspension using a red light spot. More recent generations of CO_2 laser may now be deployed via flexible fiber, and it is a good option in the pediatric population because of its low scatter and penetration [18–21].

Benign tracheobronchial obstructions can be relieved with laser endoscopic surgery. These airway stenoses are not caused by tumors per se, but can be clinically approached in a very similar manner. There are reports in pediatrics using laser therapy to manage suprastomal granulation tissue to accelerate tracheostomy tube liberation [20]. This tissue can be vaporized with any laser modality available by flexible or rigid bronchoscopy. Benign tracheal stenosis can be dealt with by endoscopically balloon dilating the stenosis after it has been incised by laser energy. Our practice has been to create two to four radial incisions in the narrowest aspects of the airway separated by intact mucosal islands before balloon dilation [20]. A smattering of other pediatric case reports demonstrate the potential for sealing off congenital tracheal abnormalities by laser treatment. Laser applications to symptomatic tracheal pouches, sealing of recurrent tracheoesophageal fistulas, repair of laryngo-tracheal clefts, splitting complete tracheal rings, debulking of endobronchial lymph nodes in tuberculosis have been reported [16, 20].

Probably the most common central airway tumor in children is tracheal papillomatosis [22]. Its management using laser therapy has been described thoroughly in the otolaryngology literature. The mainstay of management has been resection via multiple modalities with the removal of the papillomas while maintaining the underlying normal structures. Laser therapy using the carbon dioxide (CO_2) with an emission spectrum of laser has been a popular choice for the management of laryngeal, pharyngeal, and upper tracheal papillomas. Caution must be taken to evacuate the smoke plume as this gas may contain active papilloma viral particles [23].

Outside of recurrent tracheal papillomatosis, there are scattered reports of using laser photoresection to relieve other airway tumors in children when caused by inflammatory pseudotumors, endobronchial carcinoids, and hemangiomas [20]. There is potential for laser therapy to have applications to a wide-ranging set of airway lesions in pediatrics. However, the drawbacks of laser use are safety related. The laser generates heat and may strike the endotracheal tube, unaffected tissues, or ignite anesthetic gases and oxygen in the airway. The inhaled FiO_2 must be reduced to below 40% during laser activation. Most importantly, depth of penetration needs to be monitored given the thin nature of the pediatric airway as mentioned above.

Cryotherapy

Cryorecanalization and probe cryotherapy are techniques that can be used to relieve neoplastic tracheobronchial obstructions. Probe cryotherapy is an ablative technique that induces selective cell necrosis due to cellular crystallization and local microthrombi. A metal probe is used to freeze tissue by direct contact. Overlapping treatment areas using 30 second freeze–thaw cycles are used to induce cellular necrosis. Ablated tissue sloughs off and can either coughed out by the patient or manually debrided with repeat bronchoscopy 1–2 weeks post cryotherapy [24]. Cryorecanalization is a newer technique, in which the cryoprobe uses cryoadhesion to remove airway obstruction more expeditiously than does standard probe cryotherapy. We strongly suggest using cryorecanalization with a secure airway via the laryngeal mask, endotracheal intubation, or rigid bronchoscopy with total intravenous anesthesia. This facilitates the removal of specimen, frequent and rapid withdrawal and reintubation with the bronchoscope, the use of a bronchial blocker, and the desired sedation level for targeting an intraluminal lesion. Instead of treating a lesion with repeat freeze–thaw cycles, the cryoprobe is used to freeze and to adhere the lesion onto the probe. Various authors report activating the cryoprobe for anywhere between 3 and 20 seconds to achieve adherence of the obstructing lesion to the cryoprobe. After freezing and adherence, the cryoprobe is pulled away firmly from the lesion with the intent of removing and/or debulking the lesion from the airway with larger pieces than can be achieved with traditional flexible biopsy forceps. This provides large endobronchial biopsies to more rapidly relieve airway obstruction. Because of the size and frozen nature of the sample, the scope, probe, and adherent tissue are removed from the airway en bloc, and the frozen lesion is thawed in a saline basin to separate it from the cryoprobe [24] (Fig. 40.3).

This technology has become more widespread with the development of a thin and flexible cryoprobes of 1.9 mm and 2.4 mm diameters (Erbe USA, Inc., Marietta, GA). The 1.9 mm probe can be passed through the 2.0 mm working channel of an Olympus BF-P190 bronchoscope™ with proper lubrication.

Compared to laser therapy, cryorecanalization equipment is cheaper and handling does not require the special protection required for laser therapy. Additionally, in contrast to other "hot" thermal interventions like laser or electrocautery, there is no need for FiO_2 reduction. The cartilaginous and adventitial structures of the lung are protected from inadvertent extraction as they contain insufficient water content to adhere to the cryoprobe. While there is some data on bleeding complications in adults when using the cryorecanalization technique, there is no such data in children [25].

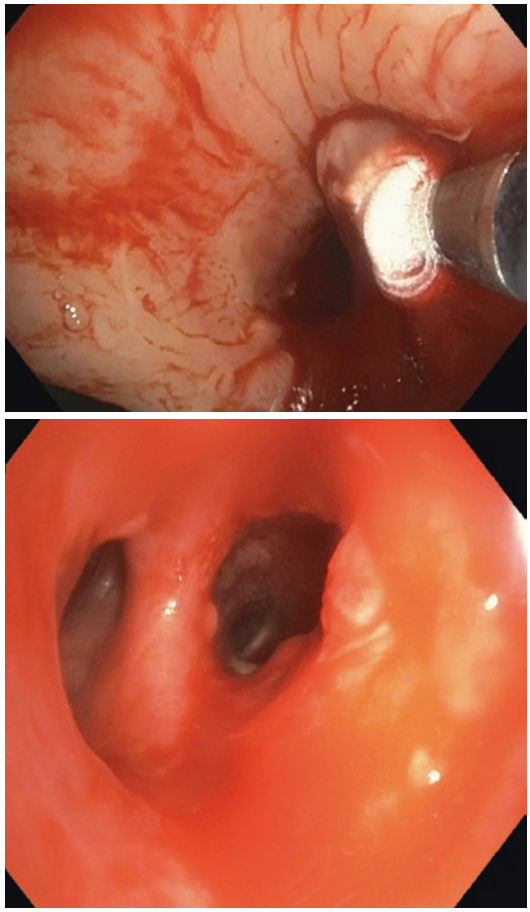

Fig. 40.3 Cryorecanalization with adhesion to tumor (top) and post en bloc removal of lesion from right mainstem bronchus (bottom)

Microdebrider

Microdebriders are constructed using a hollow tube with a rotating blade at the opening in the distal tip. Vacuum pulls tissue into the open tip and the rotating blade amputates the tissue. This makes the instrument very useful for controlled tissue removal and the suction also allows blood to be removed from the surgical field for optimal visualization [26]. The microdebrider must be used via the rigid tracheoscope, suspension laryngoscopy, or rigid bronchoscopy. In the pediatric population there are 2.9 mm, 3.5 mm, and 4 mm angled-tip laryngeal and subglottic blades (Medtronic ENT, Minneapolis, Minnesota) which are effective at removing laryngeal and tracheal papillomas without the risk of airway fire, viral particle vaporization, and increased costs associated with laser resection [27].

For this reason, the microdebrider has gained popularity for the resection of respiratory papillomas [28]. The mechanical removal of lesions avoids the laser smoke plume. Not only does it reduce the risk of transmitted viral particles, but also eliminates the thermal injury to the mucosa associated with LASER therapy. Many patients with recurrent papillomas will undergo repeated resections; therefore, avoiding repeated mucosal injury is advantageous [26]. In theory a microdebrider can be used to debulk any airway lesion or obstruction; however, attention to lesion vascularity is paramount as the cutting blades provide no hemostasis.

Argon Plasma Coagulation

Argon plasma coagulation (APC) is a noncontact, thermal ablation modality that uses argon gas to generate heat, which can be used to debride, devitalize, and debulk tissue and/or to achieve hemostasis [21]. The first use of APC in endoscopy was in 1991 and it has since been widely adopted [29].

APC uses biologically inert argon gas which flows through a tube surrounding an electrode. The delivery catheter is flexible and designed to be used via the working channel of a bronchoscope. An electrical current is applied and the resultant plasma spark generated between the end of the APC electrode (usually tungsten wire) and the tissue (about 2–10 mm) is capable of delivering high temperatures >100 °C to a depth of penetration of 2–3 mm. Because of its relatively shallow depth of penetration, APC is particularly well suited when superficial hemostasis is desired. As the treated tissue becomes dehydrated, the contact spot of the plasma on the tissue tends to move to hydrated, possibly bleeding

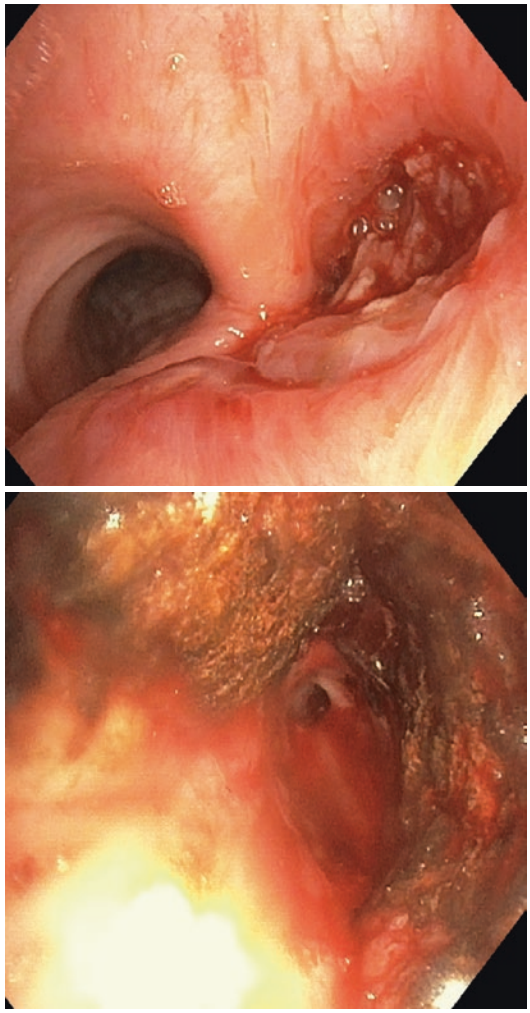

Fig. 40.4 APC used to achieve superficial hemostasis after the debridement of a vascular tumor. Pre-debridement (top) and post-debridement after APC therapy shows (bottom)

regions. The APC applicator probes come in various configurations for clinical practice including monopolar, bipolar, forward, and side firing APC probes [29, 30]. Additionally, because of its ability to desiccate and carbonize tissue, it is often used for the pre-treat vascular lesions in the airway before mechanical debridement (Fig. 40.4) [11, 29, 31].

Data in pediatrics is extremely limited, but case reports of APC being used to treat granulation tissue are available [32].

Mechanical Tumor Excision

As described above, the rigid bronchoscope can be used to intubate the pediatric airway and manage airway obstruction. The barrel of the rigid scope (Fig. 40.1) can be used to mechanically core out an airway lesion [9]. If anatomically possible, this technique allows for the fastest and most efficient return of airway patency in our experience. This technique has been described in endobronchial lesions in the pediatric airway [1].

After the bevel of the rigid barrel has been placed in the airway lumen at the level of the lesion, the bevel can be spun to excise the tumor [9]. Similarly, the rigid bevel can be used to directly create a plane because tumor and the expected border of normal airway wall. Mechanically excising an airway lesion by rigid bronchoscopy also has the advantage of facilitating other ablative techniques (all techniques listed above) via the rigid barrel itself. After physically coring of the lesion is completed, the rigid barrel can be used to traverse a large flexible scope with flexible instruments or the rigid instruments such as the microdebrider.

Conclusion

The excision of airway lesions can include many endoscopic techniques and ablative technologies. The pediatric interventional pulmonologist now has the ability to assist in the excision of airway lesions based on how large the patient's airway is, how best to manage an artificial airway during anesthesia, and the working channel size of various bronchoscopes. Understanding the local availability of each of these technologies, sizes of bronchoscopes available, rigid barrel sizes kept with the pediatric rigid bronchoscope trays at your institution, the available endotracheal tubes, and laryngeal mask airways is paramount to procedure planning. After the options have been identified based on airway limitations, the optimal technique can be determined based on the goal of the procedure, the nature of the lesion, and the anatomy of the patient.

References

1. Roby BB, Drehner D, Sidman JD. Pediatric tracheal and endobronchial tumors: an institutional experience. Arch Otolaryngol Head Neck Surg. 2011;137:925–9.
2. Eyssartier E, Ang P, Bonnemaison E, et al. Characteristics of endobronchial primitive tumors in children. Pediatr Pulmonol. 2014;49:E121–5.
3. Tischer W, Reddemann H, Herzog P, et al. Experience in surgical treatment of pulmonary and bronchial tumours in childhood. Prog Pediatr Surg. 1987;21:118–35.
4. Neville HL, Hogan AR, Zhuge Y, et al. Incidence and outcomes of malignant pediatric lung neoplasms. J Surg Res. 2009;156:224–30.
5. Hartman GE, Shochat SJ. Primary pulmonary neoplasms of childhood: a review. Ann Thorac Surg. 1983;36:108–19.
6. Hancock BJ, Di Lorenzo M, Youssef S, Yazbeck S, Marcotte JE, Collin PP. Childhood primary pulmonary neoplasms. J Pediatr Surg. 1993;28:1133–6.
7. Amini B, Huang SY, Tsai J, Benveniste MF, Robledo HH, Lee EY. Primary lung and large airway neoplasms in children: current imaging evaluation with multidetector computed tomography. Radiol Clin North Am. 2013;51:637–57.
8. DiBardino DM, Haas AR, Month RC. Interventional pulmonology. Anesthesiol Clin. 2017;35: 687–99.
9. Flannery A, Daneshvar C, Dutau H, Breen D. The art of rigid bronchoscopy and airway stenting. Clin Chest Med. 2018;39:149–67.
10. Gilbert CR, Feller-Kopman D, Akulian J, Hayes M, Yarmus L. Interventional pulmonology procedures in the pediatric population. Pediatr Pulmonol. 2014;49:597–604.
11. Gilbert CR, Wang K, Lee HJ. Interventional pulmonology in the pediatric population. Semin Respir Crit Care Med. 2014;35:751–62.
12. Rodrigues AJ, Scussiatto EA, Jacomelli M, et al. Bronchoscopic techniques for removal of foreign bodies in children's airways. Pediatr Pulmonol. 2012;47:59–62.
13. Donato L, Mai Hong Tran T, Ghori UK, Musani AI. Pediatric interventional pulmonology. Clin Chest Med. 2018;39:229–38.
14. Van Der Spek AF, Spargo PM, Norton ML. The physics of lasers and implications for their use during airway surgery. Br J Anaesth. 1988;60:709–29.
15. Rimell FL. Pediatric laser bronchoscopy. Int Anesthesiol Clin. 1997;35:107–13.
16. Fanjul M, Garcia-Casillas MA, Parente A, et al. Diode laser application for the treatment of pediatric airway pathologies. Cir Pediatr. 2008;21:79–83.
17. Patel A. Chapter 40 – Anesthesia for laser airway surgery. In: Hagberg CA, editor. Benumof and Hagberg's airway management. 3rd ed. Philadelphia: W.B. Saunders; 2013. p. 824–58.e4.
18. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008;118:1236–47.
19. Sjogren PP, Sidman JD. Use of the carbon dioxide laser for tracheobronchial lesions in children. JAMA Otolaryngol Head Neck Surg. 2013;139:231–5.
20. Eber E, Anton-Pacheco JL, de Blic J, et al. ERS statement: interventional bronchoscopy in children. Eur Respir J. 2017;50:1–19.
21. Hoag JB. Use of Medical Lasers for the Airway. In: Principles and practice of interventional pulmonology. New York: Springer; 2013.
22. Varela P, Pio L, Torre M. Primary tracheobronchial tumors in children. Semin Pediatr Surg. 2016;25:150–5.
23. Kashima HK, Kessis T, Mounts P, Shah K. Polymerase chain reaction identification of human papillomavirus DNA in CO2 laser plume from recurrent respiratory papillomatosis. Otolaryngol Head Neck Surg. 1991;104:191–5.
24. DiBardino DM, Lanfranco AR, Haas AR. Bronchoscopic cryotherapy. Clinical applications of the Cryoprobe, Cryospray, and Cryoadhesion. Ann Am Thorac Soc. 2016;13:1405–15.
25. Hetzel J, Kumpf M, Hetzel M, Hofbeck M, Baden W. Cryorecanalization of an obstructed bronchial stent in a 12-year-old boy. Respiration. 2011;82:290–3.
26. Kirse DJ. Use of the microdebrider in pediatric endoscopic airway surgery. Curr Opin Otolaryngol Head Neck Surg. 2009;17:477–82.
27. El-Bitar MA, Zalzal GH. Powered instrumentation in the treatment of recurrent respiratory papillomatosis: an alternative to the carbon dioxide laser. Arch Otolaryngol Head Neck Surg. 2002;128:425–8.
28. Schraff S, Derkay CS, Burke B, Lawson L. American Society of Pediatric Otolaryngology members' experience with recurrent respiratory papillomatosis and the use of adjuvant therapy. Arch Otolaryngol Head Neck Surg. 2004;130:1039–42.
29. Sutedja TG. Electrosurgery. In: Armin Ernst FJH, editor. Principles and practice of interventional pulmonology. New York: Springer; 2013.
30. Silvestri MAJGA. Fire and ice: laser bronchoscopy, electrocautery and cryotherapy therapy. In: Simoff MJ, Sterman DH, Ernst AA, editors. Thoracic endoscopy: advances in interventional pulmonology. 1st ed: John Wiley & Sons, Incorporated; Hoboken, New Jersey, USA: 2008. p. 378.
31. Zenker M. Argon plasma coagulation. *GMS* Krankenhaushygiene interdisziplinar. 2008; 3: Doc15-Doc.
32. Shu L, Hu Y, Wei R. Argon plasma coagulation combined with a flexible electronic bronchoscope for treating foreign body granulation tissues in children's deep bronchi: nine case reports. J Laparoendosc Adv Surg Tech A. 2016;26:1039–40.

Cryotherapy

41

Chantal Spencer Grant and Alfin Vicencio

Introduction

Cryotherapy – the application of extreme cold temperatures to tissue for therapeutic purposes – was first used in the 19th century for palliation of tumors by English physician James Arnott. Applying a mixture of salt and ice directly onto lesions with the initial intent of reducing pain and hemorrhage, Dr. Arnott discovered that the low temperatures often resulted in shrinkage of tumors. The technique evolved over time, and in 1968 cryotherapy was applied through a rigid bronchoscope to relieve an obstruction by an endobronchial tumor. By the mid-1990s, cryotherapy sparked interest from the adult pulmonary community after the development of a flexible cryoprobe that could pass through the working channel of a flexible bronchoscope [1]. Today, the availability of modern flexible bronchoscopes (specifically, smaller bronchoscopes with larger working channels), coupled with access to smaller cryoprobes, allows application of this technique in select children. Importantly, scant literature exists regarding the use of cryotherapy in children, due in part to different pathology encountered in children, and a general lack of experience among pediatric practitioners.

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In this chapter we will discuss the potential diagnostic and therapeutic roles of cryotherapy and cryoadhesion in the pediatric population.

General Principles

While the modern cryoprobe can be utilized in several clinical scenarios (discussed below), ablation of tissue has historically been a primary indication. Although cryotherapy has select advantages compared to other means of relieving airway obstructions (i.e. laser, surgery), including no blood loss (unless manual debridement is performed), no risk of airway fire, and minimal scarring, the procedure has significant downsides including delayed involution of treated lesions, frequent need for repeated procedures to achieve desired patency, and limited effect on certain tissues. Proposed mechanisms of action for cryotherapy in this regard include (1) the formation of intra- and extracellular ice crystals leading to disruption of cellular and organelle integrity, (2) dehydration and transcellular fluid shifts, and (3) local vasoconstriction and thrombosis, culminating in cell death via apoptosis or necrosis. The degree of cellular death is based in part on the temperature achieved as well as the rate of freezing. Optimal treatment requires that tissue temperature be lowered to at least −40 °C at a rate of −100 °C per minute during the time of treatment. Additional factors that affect outcomes include

S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_41

the number of freeze–thaw cycles per treatment and water content of the treated tissue. Specifically, tissue with high water content including granulation tissue, tumors, skin, and mucous membranes tend to be more cryosensitive, while, fat, cartilage, and areas of fibrosis tend to be more cryoresistant [2].

The cryotherapy apparatus (often called a cryosurgical unit or cryomachine) consists primarily of a cryogen (liquefied gas that is used to deliver cold temperatures, such as nitrous oxide or carbon dioxide), a gas container, a console to regulate flow of the cryogen, and a cryoprobe to deliver the temperatures to the desired tissue (Fig. 41.1). Cryoprobes can be of the "contact" variety (tip of the probe is directly applied to the tissue) or the "spray" variety (gas is expelled from the tip of the probe onto the desired tissue). For the purposes of this chapter, only the contact cryoprobe will be discussed. Visually, flexible cryoprobes appear similar to biopsy forceps, but the body of the probe is insulated (thereby preventing inadvertent freezing to other areas of the tracheobronchial tree as well as the bronchoscope itself), and the distal metal working tip does not open. Currently, flexible cryoprobes are commercially available in 1.9 mm and 2.4 mm diameters. Because many pediatric bronchoscopes are equipped with a 2 mm channel, the 1.9 mm probe can be utilized for select children with reasonable ease. Delivery of cold temperatures involves placing the tip of the probe directly onto the desired surface and activating release of the liquefied gas using a foot pedal. Successful application is visually obvious, as the tissue immediately surrounding the probe typically turns white within 1–2 seconds of application (Fig. 41.2).

Applications and Techniques

Cryoablation Airway obstruction by tumors is a commonly encountered problem for adult pulmonologists. In children, benign airway lesions including injury-related stenosis or congenital strictures/webs are more commonly seen. Historically, definitive therapy for such lesions has involved surgical correction. More recently, less-invasive techniques such as balloon dilation, laser division, or local corticosteroid injections have been utilized with varying degrees of

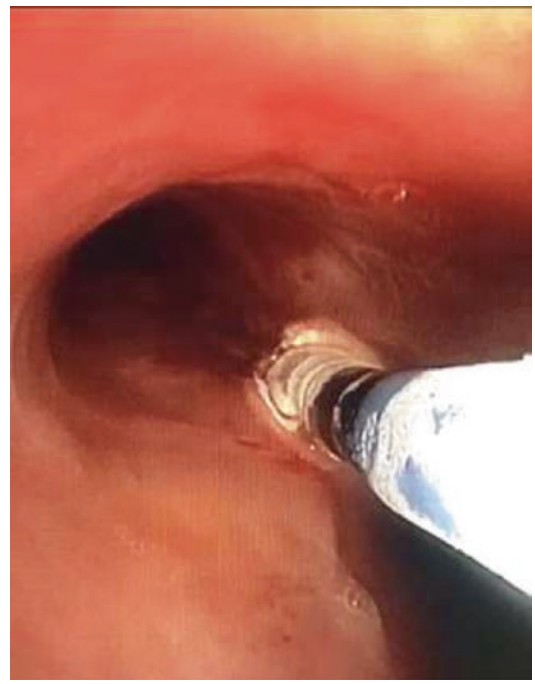

Fig. 41.2 White ring around probe tip indicates successful delivery of freezing temperatures (Spencer and Vicencio, personal archives)

Fig. 41.1 Cryotherapy apparatus. (From Erbe Medical India Pvt. Ltd. info@erbe-med.com)

success. Currently, there is no consensus on which technique represents the "gold standard," and treatment is often dictated by a combination of physician experience, nature of the obstructing lesion, and the preference of the family/patient. Cryoablation can be considered a reasonable alternative to establish airway patency in select patients, or can be used as an adjunct therapy to minimize the chance of re-stenosis following another therapeutic procedure such as balloon dilation or laser division (Fig. 41.3).

When performing cryoablation, the tip of the cryoprobe is placed directly onto the obstructing lesion and the freezing mechanism is activated via foot pedal. Upon the initiation of freezing, the tip of the probe will adhere strongly to the tissue within 1–2 seconds, and the zone of freezing will visually expand 1–3 mm beyond the tip of the probe, depending on the length of time the mechanism is activated, typically 30–60 seconds (personal preference). The mechanism is deactivated by removing pressure from the foot pedal, and can be visually confirmed by the decreasing size of the zone of freezing, followed by release of the cyroprobe tip from the tissue. The probe is then moved 2–3 mm from the initial point of treatment, and the procedure is repeated until the majority of the obstructing lesion has been treated.

Histologic examination post cryoablation of the airway is characterized by early mucosal ulceration followed by re-epithelialization with low columnar epithelium within 72 hours. Two weeks later, the mucosa appears normal but lacking cilia and goblet cells. Four weeks later, cilia and goblet cells are present [3].

Importantly, involution of the obstructing lesion following cryotherapy is typically delayed. Immediately following treatment, the obstructing lesion will appear visually unchanged, and may even appear to be more edematous. As such, cryoablation should not be attempted in patients with critical tracheal lesions unless the patient has an artificial airway distal to the area of treatment (Fig. 41.3, patient 1). Lastly, repeat treatments are often required to maximize patency.

We have found cryoablation to be particularly helpful in patients with granulomatosis with polyangiitis (GPA). Because airway obstruction in GPA is associated with progressive and recurrent multi-level airway obstruction, long-term management can be particularly challenging, often necessitating repeated and complex surgeries to maintain the patency of the airway. We previously reported the use of cyroablation to not only establish airway patency in a child with GPA, but also to prevent multilevel stenosis by employing surveillance bronchoscopy and proactively treating newly identified airway lesions before significant obstruction was established (Fig. 41.4) [4].

Cryobiopsy Flexible bronchoscopy provides a minimally invasive approach to obtain airway mucosal or lung parenchymal tissue specimens for diagnostic testing. However, obtaining adequate tissue with pediatric forceps can be challenging due to the size of the specimen obtained and the frequent presence of crush artifact. The cryoprobe may represent an alternate means to obtain biopsies in children and may in fact circumvent some of the limitations encountered with forceps biopsies. Importantly, there is scant data regarding the use of the cryoprobe in this regard for children, but there are anecdotal and significant concerns regarding safety, specifically with respect to transbronchial biopsies and risk of bleeding.

Endobronchial biopsies (EBB) are collected to evaluate the airway epithelium and mucosa. Traditionally, the procedure is performed under direct visualization, and by targeting the major and/or minor carina with standard forceps. Lesions that are located along the tracheal or bronchial wall (i.e. in parallel to the bronchoscope/forceps) can be more challenging to access due to difficulty in positioning the forceps appropriately; all too frequently, only superficial epithelial tissue is obtained. This problem can be easily circumvented with the cryoprobe. When obtaining a biopsy from the tracheal wall, the tip of the cryoprobe is simply placed directly onto

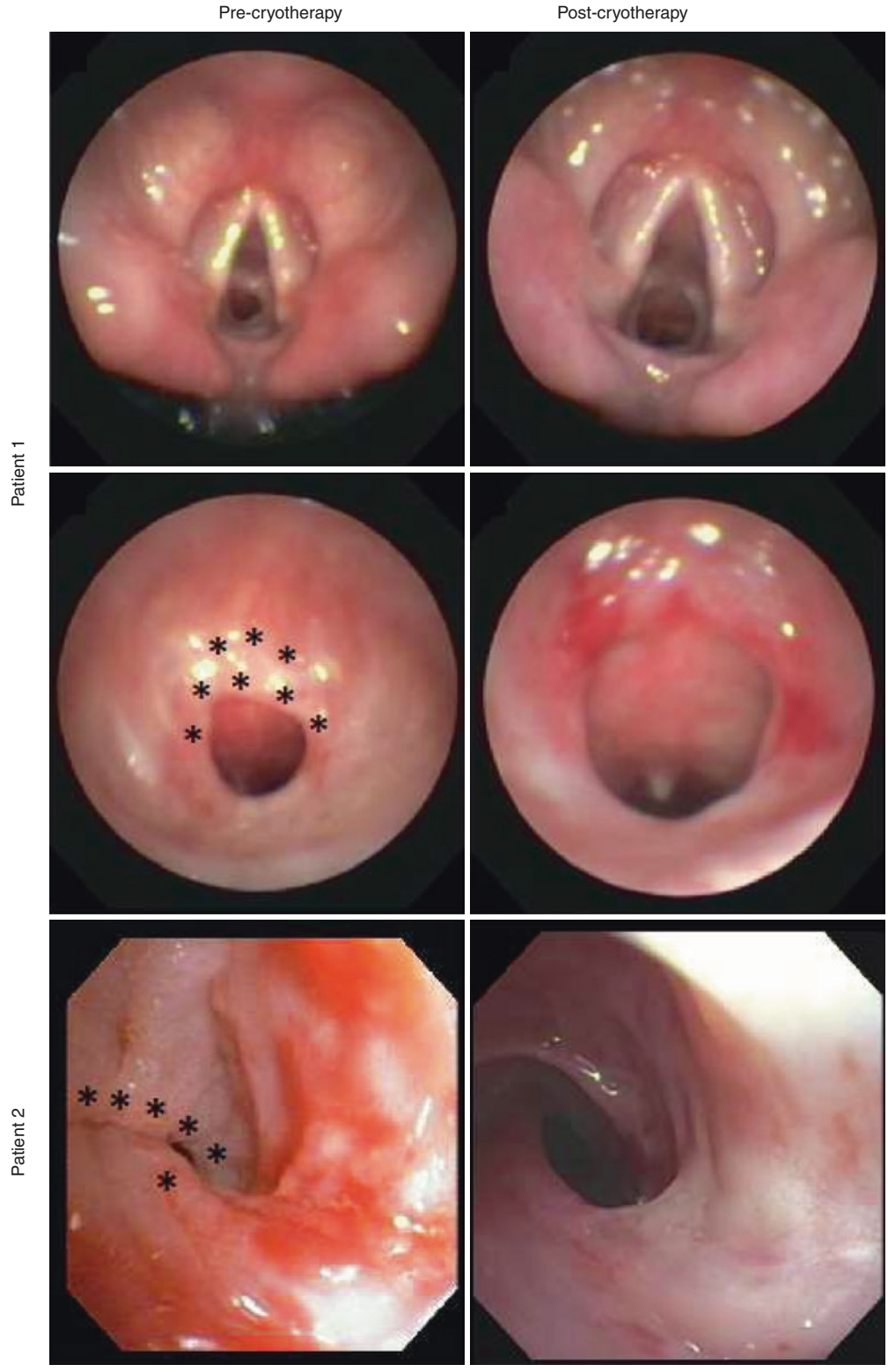

Fig. 41.3 (Patient 1) Recurrent subglottic stenosis following ballon dilation. (Patient 2) Congenital "spiral" web of the left main bronchus, unresponsive to balloon dilation (Spencer and Vicencio, personal archives)

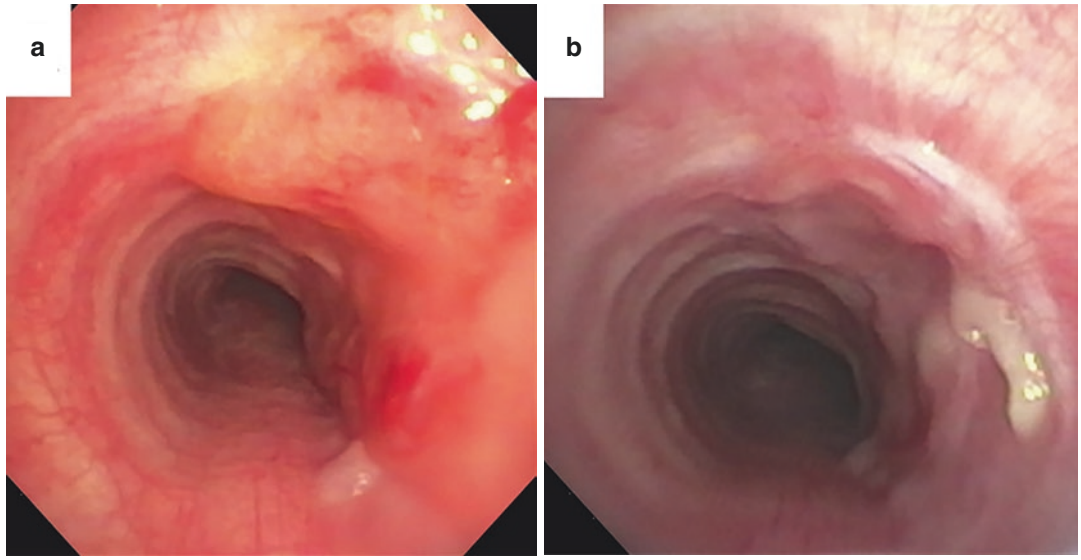

Fig. 41.4 Surveillance bronchoscopy in a patient with granulomatosis with polyangiitis identified new tracheal lesions. (**a**) pre-cryoablation, (**b**) 8-weeks post-cryoablation. (From Spencer CY, Harkin TJ, Vicencio AG. Cryotherapy to treat and prevent airway stenosis in a patient with granulomatosis with polyangiitis)

the area in question, and the freezing mechanism is activated. In doing so, the probe tightly adheres to the mucosal surface, minimizing the chance of relocation. Further, by maintaining the freezing mechanism for several seconds, the zone of freezing extends 1–3 mm beyond the probe tip, thus expanding the area and depth of the biopsy. In our practice, we maintain the freezing mechanism for 3–4 seconds before retracting the bronchoscope and cryoprobe *en bloc* to extract the specimen. The freezing mechanism is then stopped, and the specimen, now frozen and adherent to the tip of the probe, is submerged in fixative until it releases. Although scant pediatric literature exists to demonstrate the quality of specimens obtained in this manner, we previously reported the utility of this method in 3 patients with tracheal nodules [5].

Transbronchial biopsies (TBB) can be used to diagnose various pulmonary diseases, most notably transplant rejection. While the procedure plays a small role in the diagnosis of childhood interstitial lung diseases, it can be helpful for select cases with a characteristic diagnostic pattern, including granulomatous diseases or graft vs. host disease. Importantly, the histopathological usefulness of the tissue depends on size, quality, the presence of crush artifact, and the presence/absence of alveolar tissue in the specimen. TBBs obtained with forceps and are typically on the order of 0.1–0.0.3 mm^3 in size, often with little to no alveolar tissue. Recently, cryobiopsy has been proposed as an alternate method to obtain larger biopsy specimens with intact parenchymal architecture (Fig. 41.5). Previous studies comparing cryobiopsy with forceps biopsy have yielded favorable results in adults, with specimens obtained by cyrobiopsy yielding a mean diameter of approximately 7 mm (range 2–22 mm) [6]. In addition, the percentage of crush artifact that damages the pulmonary structure has been shown to be lower in cyrobiopsy specimens compared to samples obtained with conventional forceps.

Although initial reports have shown that safety of transbronchial cryobiopsy is similar to conventional TBB, there are anecdotal concerns regarding bleeding and pneumothorax. Because there are no studies evaluating the safety and utility of TBB by cryoprobe in the pediatric population, and since other methods exist to reliably and safely obtain lung tissue in children, we do not routinely employ transbronchial cryobiopsy in our practice. Future studies in both adults and

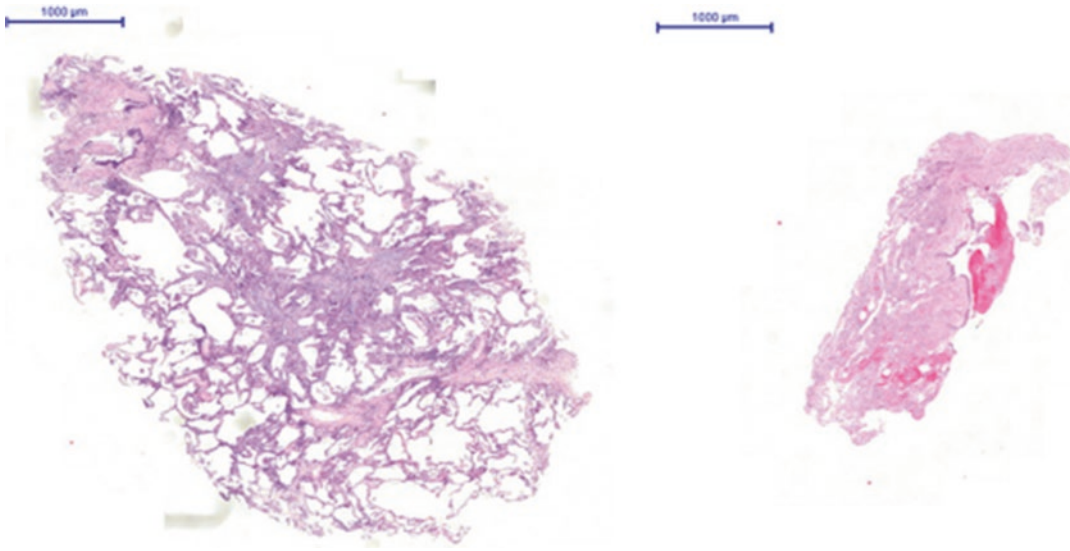

Fig. 41.5 Comparison of transbronchial biopsy specimens obtained via the cryoprobe (left) and forceps (right). (From Griff S. Schonfeld N., Ammenwerth W. et al. Diagnostic yield of Transbronchial Cryobiopsy in Non-Neoplastic Lung Disease: A Retrospective Case Series)

children are required before any formal recommendations are proposed.

Foreign Body Removal Flexible bronchoscopy is increasingly used to safely and effectively remove airway foreign bodies in children. Although numerous tools exist to facilitate foreign body removal via flexible bronchoscopy (forceps, retrieval baskets, and tri-tip graspers), recent literature highlights the potential utility of the cryoprobe. The technique, commonly termed cryoadhesion, involves placing the tip of the probe on the surface of the foreign object, activating the freezing mechanism to achieve adhesion (similar to placing one's tongue on a frozen metal surface), and removing the bronchoscope, probe, and foreign object *en bloc*. Depending on the characteristics of the obstructing object, cryoadhesion may prove ideal for select patients. For example, this method is particularly helpful for removing foreign bodies with smooth or flat surfaces, which are often difficult to grasp with forceps. We have found that cryoadhesion greatly facilitates removal of blood clots and inflammatory casts. Lastly, the cryoprobe can be easily inserted into very small diameter bronchi to remove fragmented objects that have migrated distally, without the need to position forceps around the object.

Summary

The recent availability of cryoprobes suitable for use in children has begun to expand the discipline of interventional pediatric bronchoscopy. Although few pediatric bronchoscopists have extensive experience with these techniques, it seems inevitable that such procedures will become more commonplace in the near future.

Bronchoscopic Cryotherapy

- Abstract
- Keywords
  Pediatric; bronchoscopy; cryoadhesion; cryotherapy; cryobiopsy
  airway obstruction
- *General Principles*
  - Cryotherapy/cryoadhesion and cryobiopsy
  - Mechanism of action (uptodate and DiBardino 2016)
  - Equipment
  - Technique
  - Photos of cryomachine (bronchoscopic cryo ATS 2016 Fig. 41.1a, d)
- *Cryobiopsy*
  - Benefits
    Crush artifact

Size
Photo of biopsy size comparison, Griff 2011
– How to perform
– Endobronchial biopsy
Airway masses
Tracheal lesions and bronchial lesions
– Transbronchial biopsy
Diagnosis of parenchymal lung disease (little peds data or case reports, adult data from Pajares 2014)
Lung transplant surveillance data

- *Cryoadhesion*
  - *Foreign Body Removal*
    General techniques used for FB removal
    Benefits of cryoadhesion
    How to perform (Kazachov 2016; Fruchter, 2015)
    Inorganic and organic objects, high water content vs. low water content
    Plastic bronchitis
    Adjunct therapeutic procedure for retained FB embedded in granulation
    Safety/cons (Zhang, 2016)
- *Cryoablation*
  - *Non-Critical Airway obstruction*
  - Principles (DiBardino 2016; Mathur 1996)
  - Treatment of granulation tissue
  - Rheumatologic disorders (treatment and prevention of lesions). Add photos from case report
  - AAIR syndrome (site Pediatrics article)
  - Adjunct therapy to balloon dilation
- *Cryo-Rrelated Complications*
  - Hemorrhage
  - Airway perforation
  - Airway edema

References

1. DiBardino DM, Lanfranco AR, Haas AR. Bronchoscopic cryotherapy: clinical applications of the cryoprobe, cryospray, and cryoadhesion. Ann ATS. 2016;13(8):1405–15.
2. Pajares V, Puzo C, Castillo D, Lerma E, Montero MA, Ramos-Barbon D, Amor-Carro O, Gil de Bernabe A, Franquet T, Plaza V, Hetzel J, Sanchis J, Torrego A. Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. Respirology. 2014 Aug;19.
3. Kazachov M, Vicencio A. Foreign body removal is getting "cooler". Pediatr Pulmonol. 2016 Sept;51.
4. Fruchter O, Kramer MR. Retrieval of various aspirated foreign bodies by flexible cryoprobe: in vitro feasibility study. 2015 Clin Respir J. Apr;9.
5. Zhang L, Yin Y, Zhang J, Zhang H. Removal of foreign bodies in children's airways using flexible bronchoscopic CO2 cryotherapy. Pediatr Pulmonol. 2016;51:943–9.
6. Mathur PN, Wolf KM, Busk MF, Briete WM, Datzman M. Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. Chest. 1996 Sept;110

Bibliography

1. S. R. Principles and practice of interventional pulmonology. New York: Springer; 2013.
2. Talbert JL, Rodgers BM. Clinical application of endotracheal cryotherapy. J Pediatr Surg. 1978;13:662–8.
3. Spencer CY, Harkin TJ, Vicencio AG. Cryotherapy to treat and prevent airway stenosis in a patient with granulomatosis with polyangiitis. Pediatr Pulmonology. 2018;53:1.
4. Spencer CY, Millman J, Veiga K, Vicencio AG. Airway Autoimmune Inflammatory Response (AAIR) syndrome: an asthma- autoimmune overlap disorder? Pediatrics. 2018;141(3):e20170138.
5. Griff S, Schönfeld N, Ammenwerth W, Blum T-G, Grah C, Bauer TT, Grüning W, Mairinger T, Wurps H. Diagnostic yield of transbronchial cryobiopsy in non-neoplastic lung disease: a retrospective case series. BMC Pulm Med. 2014;14:171.
6. Pourabdollah M, Shamaei M, Karimi S, Karimi M, Kiani A, Jabbari HR. Transbronchial lung Biopsy: the pathologist's point of view. Clin Resir J. 2016;10:2011–216.

Bronchial Thermoplasty

42

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Introduction

Asthma is one of the most common respiratory diseases, estimated to occur in over 8% of children [1]. Severe persistent asthma is defined as asthma that remains poorly controlled despite treatment with appropriate controller medications including inhaled corticosteroids and long-acting beta-agonists, or dependence on chronic oral steroids to control their disease [2]. About 10% of children with asthma are considered to have severe persistent disease [2, 3] and those with poorly controlled or refractory asthma despite appropriate therapy are at risk for many long-term adverse events related to their disease, as well as other significant impacts on their overall health [2, 4].

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Updates in Asthma Therapy

In the United States in 2007 alone, the cost of asthma was estimated to be over 56 million dollars, including health care costs and lost work time [5]. Those with severe asthma account for the majority of this cost; severe asthma in children is associated with a higher cost burden including a significant number of missed school days compared to their peers, which impacts their education, and results in lost work time for their caregivers [3–7]. Newer guidelines and treatment modalities have been developed over the last several years, with a shift from a more "one size fits all" approach to treating asthma to a focus on phenotyping disease in children and adults with asthma [4, 6]. Different characteristics, triggers, or inflammatory responses may respond differently to certain therapies, suggesting that targeted therapy may be an approach to controlling disease and decreasing exacerbations [4, 6]. The US Food and Drug Administration (FDA) has recently approved three new biologic drugs (monoclonal antibodies) for use in children and adults with asthma, each targeting different types of airway inflammation [8]. Omalizumab was the first to be approved, which is an anti-IgE monoclonal antibody and appears to have the most benefit in children and adults with predominantly allergic asthma with elevated IgE levels; it is currently approved for use in children 6 years and older and adults [9, 10]. Mepolizumab was the second to be

S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_42

approved [11, 12], followed by reslizumab [13, 14], both anti-IL 5 monoclonal antibodies. Currently, benralizumab is approved for adolescents and adults 12 years and older, resilzumab for adults 18 years and older, and mepolizumab and omalizumab for age 6 years and older at this time [9, 11, 13]. There are specific criteria for eligibility for these therapies, and they are often used after children are unable to be controlled with other standard therapies, including inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA). In addition, the cost of these drugs is high and often require chronic injections in order to provide adequate dosing [15].

Biologic therapy shows promise in reducing medication burden, decreasing severe exacerbations, and improving quality of life in both children and adults [4, 15–17]. Unfortunately, not all children meet eligibility criteria for one of these drugs despite disease characteristics that may respond to these therapies. Some children continue to have significant disease burden despite the use of biologic therapy. In addition, these drugs are expensive, require frequent and long-term administration, and not all children who are eligible for therapy receive it.

Rationale for Using Bronchial Thermoplasty

Bronchial thermoplasty (BTP) is a procedure which is FDA-approved for use in adults with severe asthma. It has been shown to decrease the frequency of severe exacerbations and emergent health care visits in adults with severe asthma for several years following the procedure [18–20]. The procedure utilizes bronchoscopy to deliver targeted radiofrequency energy to large airways, resulting in ablation of smooth muscle [18]. Computed tomography (CT) imaging of the lungs of children and adults with severe asthma has demonstrated a significant increase in wall thickness and wall area, specifically in the third-generation airways (first segmental branches) compared to healthy controls as well as children and adults with mild-to-moderate asthma. This increase in airway thickness and area is maintained over time and inversely correlated with baseline FEV1% predicted [21]. Biopsies from airways of children and adults with asthma show a pathologic increase in smooth muscle tissue in the large- and medium-sized airways, resulting in increased bronchoconstriction and mucus production and secretions, causing symptoms characteristic of asthma exacerbations [22]. Over time, this increased smooth muscle mass can result in abnormal airway remodeling, potentially leading to fixed airway obstruction, pulmonary scarring, and fibrosis [23, 24].

BTP uses radiofrequency energy to directly target large–medium bronchi to 3 mm airways. Studies of airway smooth muscle show that reactivity is dramatically decreased or even eliminated after just a few minutes of heat application (~60C) [25]. It is speculated that the increased temperature results in denaturation of muscle tissue and disrupts the actin-myosin connections, which limits the ability of the airways to constrict in response to known triggers [25]. A clinical study using biopsies from adults who have undergone BTP demonstrated a 48–78% decrease in smooth muscle mass in the treated airways, which held up in additional subsequent studies [26, 27]. Not only was there decreased muscle mass in the treated airways, the initial study showed a 50% decrease in adjacent airways that were not directly treated with radiofrequency energy [27]. In addition to evaluating smooth muscle mass, researchers investigated other factors that contribute to airway reactivity, showing that BTP resulted in decreased nerve endings, type I collagen fibers, and inflammatory markers like transforming growth factor-beta (TGF B) and chemokine ligand 5 (CCL5) [28]. Moreover, a reduction in airway smooth muscle may have a systemic influence on airway remodeling, including altering the expression genes associated with eosinophilic inflammation and T cell activation [26, 28].

Clinical Safety and Efficacy of BTP

There have been several studies demonstrating the safety and clinical efficacy of BTP in adults, ranging from those with mild-to-moderate dis-

ease to those with more moderate-to-severe disease [19, 29–33]. The Asthma Intervention Research (AIR) trial was a multi-site randomized controlled prospective study that evaluated the safety and efficacy of BTP in adults with moderate-to-severe asthma. These adults all required ICS plus LABA to maintain adequate control of their asthma, and all demonstrated a decrease or loss of control when the LABA was removed [34]. One hundred and twelve subjects were randomized to either an intervention group (BTP) or a control group (standard of care with ICS + LABA). The primary outcome was the frequency of mild acute asthma exacerbations after the LABA was removed. In the intervention group, adults showed a decrease in the mean rate of mild asthma exacerbations compared to the control group [34]. Secondary endpoints were also improved in the BTP group compared to standard of care, including improvements in morning peak expiratory flow, increase in percentage of symptom free days, and subjective improvement in the Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) that were sustained over the year following BTP [34]. BTP was not without complications though, as there were more hospitalizations for worsening asthma symptoms in the BTP group compared to the control group in the immediate post-intervention period, but no increase in adverse events in the 6 weeks to 12 months post-intervention follow-up period. Based on these data, the researchers concluded that BTP resulted in improvement in asthma control, though they did note that there was likely a large placebo effect as neither subjects nor providers were blinded to the intervention [34].

The Research in Severe Asthma (RISA) study was another multi-center, randomized controlled, non-blinded clinical trial that evaluated the safety and efficacy of adults who remained symptomatic from their asthma despite treatment with high-dose ICS plus LABA and other medications (chronic oral steroids, leukotriene receptor antagonists, theophylline) [31]. In this study, 32 adults were randomized to BTP or control (no intervention, continuation of standard of care) group. Those that were randomized to BTP received three BTP treatments at least 3 weeks apart and remained on their baseline asthma control medications. Following the intervention period, all subjects entered a 16-week steroid stable phase, during which they were continued on their baseline medications. After these 16 weeks, there was a 14-week corticosteroid wean phase followed by a 16-week reduced corticosteroid extension phase, during which attempts to wean or decrease corticosteroid dosage (either oral or inhaled) were made. As in the AIR trial, there was an increase in adverse respiratory events (including wheezing, cough, dyspnea, and chest tightness) immediately following BTP in the intervention group, but no difference in the follow-up period [31]. In the steroid-stable phase, subjects who underwent BTP reported a significant decrease in rescue medication usage compared to baseline, as well as improvements in pre-bronchodilator FEV1% predicted and AQLQ scores compared to the control group. While there was no significant difference in the ability of subjects to completely wean or decrease their steroid usage during the reduced steroid phase, those who had undergone BTP continued to report decreased rescue medication use and increased AQLQ scores. These researchers concluded that adults with symptomatic severe asthma could safely tolerate BTP, and that although the study was small, there appeared to be improvements in quality of life and rescue medication usage, suggesting that BTP may be an additional treatment option for adults with severe asthma [31].

The AIR2 trial was similar to the RISA trial with the addition of a “sham procedure” arm as the control group to evaluate safety and efficacy of BTP in adults who continued to have severe symptomatic asthma despite treatment with appropriate medical therapy. By utilizing a sham procedure, in which the procedure was identical to the intervention procedure with the exception of delivery of RF energy, the researchers were able to blind both the subjects and the study investigators to the intervention to remove potential confounding caused by a placebo effect [35]. In this trial, 288 subjects dependent on high-dose ICS + LABA were randomized 2:1 to either the BTP or sham group. All subjects underwent three

bronchoscopy procedures at least 3 weeks apart; the primary outcome for this study was the difference between the AQLQ score change in the two groups compared to baseline. Adults in the BTP group had a greater increase in their AQLQ scores compared to baseline at each assessment in the year following BTP compared to the sham group. Those receiving BTP also had a decrease in severe exacerbations and emergency room visits compared to the sham group, though there was no difference in the rate of hospitalizations or unscheduled outpatient visits. Finally, as in the prior two studies discussed, there were more adverse events (wheezing, cough, chest discomfort) in the BTP group than the sham group in the immediate post-intervention phase, but a decrease in adverse respiratory events in the BTP group during the follow-up period [35].

Long-Term Effectiveness of BTP in Adults

Long-term effectiveness and persistence of effects of BTP has been demonstrated as well. Subjects in the RISA trial were followed annually for 5 years after their intervention. Analysis showed that adults that underwent BTP had a 68% decreased rate of hospitalization in the 5 years post-BTP but no statistically significant decrease in Emergency Department visits for respiratory symptoms [32]. While these subjects did not have significantly decreased medication usage, pulmonary function testing revealed slightly improved FEV1% predicted that remained stable in the 5 years following the procedure. Most importantly, there were no significant respiratory adverse events during the follow-up period [32].

Subjects that participated in the AIR2 trial were studied at 2 years and 5 years after their procedure. In the two-year follow-up, subjects demonstrated a sustained effect from BTP, including decreased rate of severe exacerbations, decreased asthma-related adverse events, and decreased emergency room visits and hospitalizations [36]. The AIR2 five-year follow-up evaluated the sustainability of any benefits or improvements from BTP in the 5 years following the intervention [20]. In this analysis, the proportion of adults that suffered a severe exacerbation was not statistically different over the 5 years post-treatment, but there was an average decrease of severe exacerbations by 44% compared to the year prior to BTP [20]. The decrease in the rate of Emergency Department visits for asthma-related symptoms that was seen in the first year after treatment was maintained over 5 years, and the initial improvement in pre-bronchodilator FEV1% predicted was sustained and stable over the follow-up period [20].

In the ongoing PAS2 (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma) study, an interim analysis of 190 subject was done 3 years after the initial intervention and compared to the AIR2 follow-up analysis. The primary endpoint was the number of subjects experiencing a severe asthma exacerbation in each 12-month period compared to the year prior to BTP [30]. While approximately 40% of adults experienced at least one severe exacerbation during the third year of follow-up, there was nearly a 45% relative decrease in the frequency of severe exacerbations in the intervention group, similar to that found in the AIR2 trial. As in the AIR2 follow-up, subjects who underwent BTP were able to significantly decrease their ICS dosage, but there was also a greater decrease in those dependent on daily oral corticosteroids for asthma management in the PAS2 trial that was not previously seen in the AIR2 group. Finally, there was a significant decrease in emergency room visits in the intervention group at 3 years, but no change in hospitalizations or lung function, similar to AIR2 [20, 30]. Subjective measures like the AQLQ were not collected during this study [30].

Considerations for BTP in Children

While BTP has shown promise in adults with severe persistent asthma despite appropriate medical therapy, it is not currently FDA-approved for use in children. The procedure is currently indicated for adults 18 years old or older with

severe persistent asthma that is not well controlled with ICS + LABA [8]. As mentioned previously, newer biologic medications targeting specific parts of the inflammatory cascade have improved the quality of life and symptom control in some children, but not all children are eligible for or respond to these therapies [4, 12, 37]. In addition, some adolescents with severe disease are dependent on chronic (daily or every other day) oral steroid use, which can lead to adrenal insufficiency, glucose instability, and other adverse effects of the drug. Poorly controlled disease with persistent symptoms or frequent exacerbations results in increased missed days of school, impacting their education and their caregiver's work schedule, increasing the overall burden of asthma [3]. Given that multiple studies have demonstrated a sustained effect of BTP in adults, it could be considered as an intervention in children with some modifications and additional considerations [19, 35, 36].

There are certainly limitations on which children would be eligible for BTP therapy and concerns about long-term effects as this is still an emerging modality in adults. The radiofrequency probe delivers thermal energy directly to the airway wall but in adults does not come into contact with the entire airway wall [8]. The probe needs to fit through the working channel of the bronchoscope, and at this time the probe cannot fit through a channel smaller than 2.0 mm. The channels on the 2.8 mm and 3.1 mm bronchoscopes commonly used in pediatrics are only 1.2 mm in diameter. The airways need to be large enough to allow for direct visualization of delivery of the RF energy as the probe extends beyond the end of the bronchoscope. This would likely result in only adolescents being large enough to tolerate this size of bronchoscope. Furthermore, there is also concern that BTP therapy could limit airway size in young children who have not reached their maximum potential lung growth.

In many centers, bronchial thermoplasty is typically done as an outpatient procedure in an endoscopy suite with adults receiving "conscious sedation" rather than general anesthesia. An artificial airway is often used in adults, such as a laryngeal mask airway (LMA), for patient safety and for stability during the BTP procedure. Since the LMA does not come into direct contact with the lower airways like an endotracheal tube does, it may have less-associated inflammation within the larger airways that could lead to worsening bronchospasm or inflammation. Topical anesthetic (lidocaine) is used to decrease the cough reflex, and often an anti-sialorrheic medication (such as glycopyrrolate) is used to decrease airway secretion production and release. It is also important to ensure the patient's asthma is stable in the few weeks leading up to the procedure and that they are at their asthma baseline in terms of symptoms and medications. Failing to do this increases the risk of adverse events and exacerbations following the procedure. Adults are treated with a course of oral steroids (at a dose equivalent to that used during an acute exacerbation) beginning prior to the procedure and continuing at least through the day after the procedure to help decrease airway hyperreactivity that occurs as a result of BTP. Pulmonary function testing is performed following BTP, and patients are discharged the same day once they have demonstrated stability in their lung function [38].

At our center, as at many other large academic pediatric centers, flexible bronchoscopy is performed under general anesthesia; there are no contraindications to the use of general anesthesia for pediatric BTP therapies. It is not unusual for children with asthma to have difficulty tolerating sedation; up to about 30% can have transient hypoxemia or require bronchodilators while under anesthesia, even when not undergoing an airway or pulmonary procedure [39]. LMAs and topical lidocaine are also typically used in pediatric procedures. It is also important to ensure the child's asthma is stable prior to the procedure as some adolescents with severe asthma often do not have several weeks of stability without exacerbations or they have difficulty recognizing their symptoms, so they may not be able to safely tolerate the procedure or may be at increased risk of adverse events following the procedure.

Spirometry or additional pulmonary function testing prior to BTP intervention may also be useful to ensure that a child's asthma is stable. It may be prudent to extend the course of oral ste-

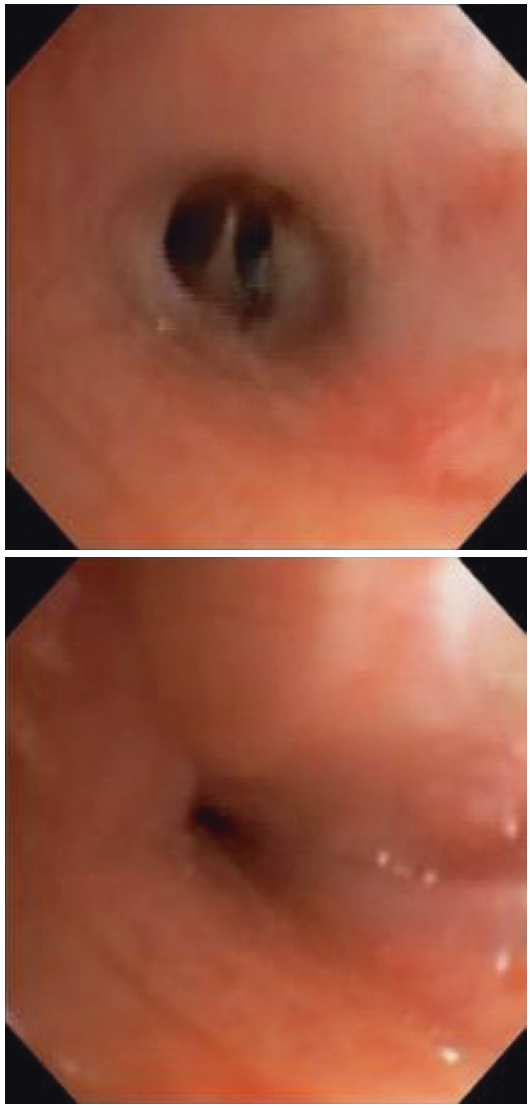

Fig. 42.1 Concentric narrowing of a left upper lobe subsegmental bronchus during the bronchoscopic procedure of a child with asthma

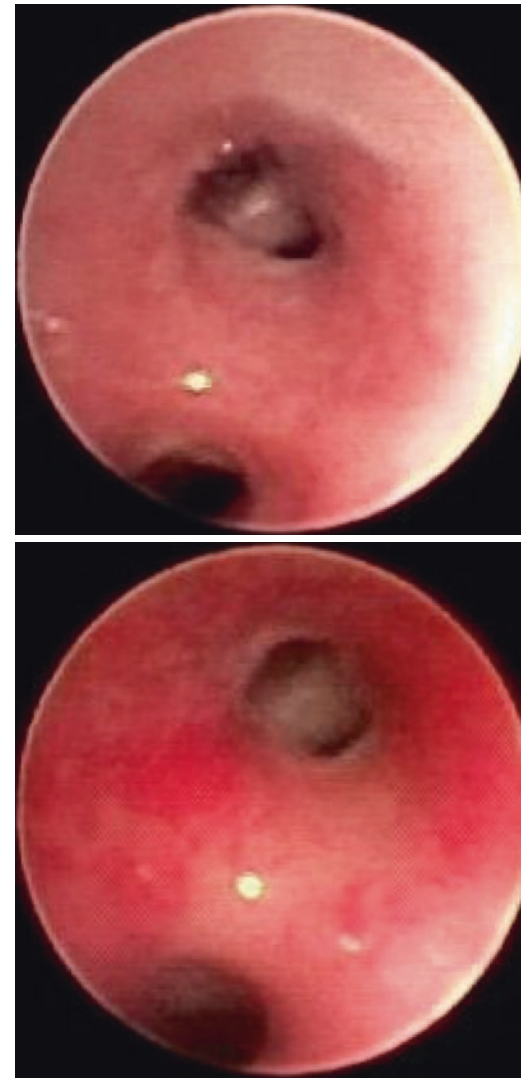

Fig. 42.2 Inflamed left upper lobar bronchus with mucosal trauma with vigorous coughing during bronchoscopic procedure of a child with asthma

roids following the procedure similar to that used in adults. Experience at our center has shown that many children with asthma will have bronchoconstriction that can be directly visualized during the procedure (see Fig. 42.1), as well as increased cough and wheeze as a result of bronchoscopy alone (see Fig. 42.2), which may worsen with interventions that increase airway inflammation (see images). In addition, we would recommend a low threshold for admission for observation following the procedure, as many adolescents with asthma have decreased symptom perception which increases the risk of serious adverse events related to asthma exacerbations.

Potential Modifications to the BTP Procedure in Children

There are many studies and trials utilizing ultrashort echo time magnetic resonance imaging (UTE MRI) and hyperpolarized gases (namely helium and xenon) to better understand respiratory mechanics and physiology in certain disease states, such as cystic fibrosis and asthma [40, 41]. Aysola et al. have shown that there is a regional distribution to ventilation defects, and that some areas of the lung appear to be more affected by the disease than others [42], and areas of ventilation defects seen on MRI corresponded to areas of air trapping seen on CT scans [43]. Studies using hyperpolarized helium and xenon combined with MRI have been done in children with asthma that show that there are non-uniform ventilation defects within the lungs [40, 44, 45], while other studies have shown that in children with asthma, large areas of ventilation defects were seen only in children with severe asthma and not in those with only mild-to-moderate disease. The children with larger ventilation defects had more severe disease, a higher medication dependence, and decreased FEV1%predicted than children with fewer defects [21, 46]. A study done by Thomen et al. attempted to quantify regional ventilation in the lungs with both MRI and CT in healthy adult controls and adults with severe asthma and evaluate changes in regional ventilation before and after BTP treatments in the adults with asthma [43]. In this study, they found that healthy adults without asthma had very little regional variation in ventilation, but those with asthma had larger segmental differences in ventilation. The majority of adults with asthma then underwent BTP and were re-imaged with hyperpolarized MRI. Following the intervention, the differences in regional ventilation distribution disappeared or became much smaller and more closely approximated ventilation differences seen in the healthy adults [43]. While this study had a small sample size, it demonstrated that it is possible to quantify regional ventilation within the lung using MRI, which may provide a long-term method for evaluating and understanding a patient's disease without exposure to significant amounts of radiation.

In the adult studies described above, all subjects underwent three different BTP procedures at least 3 weeks apart, with each treatment focusing on a different part of the airway (right lower lobe, followed by left lower lobe, then the bilateral upper lobes; the right middle lobe was not treated during these procedures) [18–20, 29–31, 35]. Imaging studies, including MRI, are being used as a marker of asthma, demonstrating that there are areas with ventilation differences within the lungs, suggesting a greater disease burden [47]. Based on this, BTP therapy targeting the areas of greater ventilation differences may be a future direction of study. As discussed above, treating all the large airways in children raises concern for impacts long-term growth and remodeling of the lungs and airways. The information obtained with MRI can identify the regions of the lung that may be contributing the most to asthma symptoms and exacerbations. If there is a significantly larger ventilation difference in a particular lobe or segment, that area can be treated first with BTP. This could potentially decrease the number of treatments that children would need to undergo while still providing symptomatic improvement. In addition, using a targeted approach to treat the most affected airways could decrease the adverse event profile in adolescents while still providing them with clinical benefit. Based on their response and overall clinical status, additional treatments could be performed as necessary and guided by follow-up MRI imaging.

BTP is still an emerging therapy in adults with severe persistent asthma, and while long-term follow-up studies have shown persistence of effectiveness, there is still much to learn about the effects on airway growth and remodeling [20, 30]. Post-pubertal adolescents are typically done or mostly done with linear growth and therefore most of their growth of lung size; however, the effects

on further alveolar development and remodeling is unclear, especially given the studies that suggest that there may be some systemic effects of BTP. On the other hand, studies have shown that there is decreased airway smooth muscle mass in adjacent untreated airways, which may indicate that fewer treatments or shorter treatments may still be beneficial in adolescents [27].

BTP is indicated for the treatment of severe persistent asthma in patients over 18 years, whose asthma is not well controlled with standard therapy including ICS and LABA and should not be performed in those with implantable electronic devices (i.e., pacemakers), sensitivity to medications used during the procedure, those with active respiratory infections or asthma exacerbations, recent adjustments in asthma control medications, or coagulopathies [8]. Given that the long-term effects of BTP are not fully understood to date, it would be prudent to reserve this procedure for adolescents that have severe persistent disease despite adequate therapy, or for those children who continue to have uncontrolled symptoms and/or frequent severe exacerbations after treatment with newer targeted biologic therapies, as these children do not have many available treatment options left other than high dose inhaled corticosteroids and/or systemic corticosteroid treatment, which carry significant adverse events. As this procedure becomes more utilized in adults, studies will need to be done to determine if there are factors that predict a response to BTP, and if so, identify which are relevant to the adolescent population.

References

1. Centers for Disease Control and Prevention. 2014 National Health Interview Survey (NHIS) data; Table 4-1 Current asthma prevalence percents by age, United States: National Health Interview Survey [Available from: https://www.cdc.gov/asthma/nhis/2014/table4-1.htm.
2. Ramratnam SK, Bacharier LB, Guilbert TW. Severe asthma in children. J Allergy Clin Immunol Pract. 2017;5(4):889–98.
3. Wenzel S. Severe asthma in adults. Am J Respir Crit Care Med. 2005;172(2):149–60.
4. Burg GT, Covar R, Oland AA, Guilbert TW. The tempest: difficult to control asthma in adolescence. J Allergy Clin Immunol Pract. 2018;6(3):738–48.
5. Centers for Disease Control and Prevention. Asthma in the US [Available from: https://www.cdc.gov/vitalsigns/asthma/.
6. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343–73.
7. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007;119(2):405–13.
8. Asthmatx Inc. Alair Bronchial Thermoplasty System Operator's Manual.
9. Genetech. FDA label for omalizumab [July 31, 2018]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf.
10. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics. 2001;108(2):E36.
11. Teva Pharmaceutical Industries Ltd. FDA label for reslizumab.
12. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198–207.
13. GlaxoSmithKline. FDA label for mepolizumab [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125526s004lbl.pdf.
14. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med. 2011;184(10):1125–32.
15. Lai T, Wang S, Xu Z, Zhang C, Zhao Y, Hu Y, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. Sci Rep. 2015;5:8191.
16. Liu Y, Zhang S, Li DW, Jiang SJ. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. PLoS One. 2013;8(3):e59872.
17. Lim HF, Nair P. Efficacy and safety of reslizumab in patients with moderate to severe eosinophilic asthma. Expert Rev Respir Med. 2015;9(2):135–42.
18. Sheshadri A, Castro M, Chen A. Bronchial thermoplasty: a novel therapy for severe asthma. Clin Chest Med. 2013;34(3):437–44.
19. Castro M, Musani AI, Mayse ML, Shargill NS. Bronchial thermoplasty: a novel technique in the treatment of severe asthma. Ther Adv Respir Dis. 2010;4(2):101–16.
20. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, et al. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol. 2013;132(6):1295–302.

21. Aysola RS, Hoffman EA, Gierada D, Wenzel S, Cook-Granroth J, Tarsi J, et al. Airway remodeling measured by multidetector CT is increased in severe asthma and correlates with pathology. Chest. 2008;134(6):1183–91.
22. Bergeron C, Boulet LP. Structural changes in airway diseases: characteristics, mechanisms, consequences, and pharmacologic modulation. Chest. 2006;129(4):1068–87.
23. Cohen L, E X TJ, Ramkumar T, Horiuchi TK, Cochran R, et al. Epithelial cell proliferation contributes to airway remodeling in severe asthma. Am J Respir Crit Care Med. 2007;176(2):138–45.
24. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med. 2000;161(5):1720–45.
25. Dyrda P, Tazzeo T, DoHarris L, Nilius B, Roman HN, Lauzon AM, et al. Acute response of airway muscle to extreme temperature includes disruption of actin-myosin interaction. Am J Respir Cell Mol Biol. 2011;44(2):213–21.
26. Chakir J, Haj-Salem I, Gras D, Joubert P, Beaudoin EL, Biardel S, et al. Effects of bronchial thermoplasty on airway smooth muscle and collagen deposition in asthma. Ann Am Thorac Soc. 2015;12(11):1612–8.
27. Pretolani M, Dombret MC, Thabut G, Knap D, Hamidi F, Debray MP, et al. Reduction of airway smooth muscle mass by bronchial thermoplasty in patients with severe asthma. Am J Respir Crit Care Med. 2014;190(12):1452–4.
28. Denner DR, Doeing DC, Hogarth DK, Dugan K, Naureckas ET, White SR. Airway inflammation after bronchial thermoplasty for severe asthma. Ann Am Thorac Soc. 2015;12(9):1302–9.
29. Castro M, Cox G. Asthma outcomes from bronchial thermoplasty in the AIR2 trial. Am J Respir Crit Care Med. 2011;184(6):743–4.
30. Chupp G, Laviolette M, Cohn L, McEvoy C, Bansal S, Shifren A, et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. Eur Respirat J. 2017;50:(2)1700017.
31. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. Am J Respir Crit Care Med. 2007;176(12):1185–91.
32. Pavord ID, Thomson NC, Niven RM, Corris PA, Chung KF, Cox G, et al. Safety of bronchial thermoplasty in patients with severe refractory asthma. Ann Allergy Asthma Immunol. 2013;111(5):402–7.
33. Pretolani M, Bergqvist A, Thabut G, Dombret MC, Knapp D, Hamidi F, et al. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathologic correlations. J Allergy Clin Immunol. 2017;139(4):1176–85.
34. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med. 2007;356(13):1327–37.
35. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010;181(2):116–24.
36. Castro M, Rubin A, Laviolette M, Hanania NA, Armstrong B, Cox G. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. Ann Allergy Asthma Immunol. 2011;107(1):65–70.
37. Katial RK, Bensch GW, Busse WW, Chipps BE, Denson JL, Gerber AN, et al. Changing paradigms in the treatment of severe asthma: the role of biologic therapies. J Allergy Clin Immunol Pract. 2017;5(2S):S1–S14.
38. Sood S, Hall CB, Castro M. Imaging procedures and bronchial thermoplasty for asthma assessment and intervention. In: Szefler SJ, Wechsler ME, Holguin F, editors. Personalizing asthma management for the clinician. St. Louis: Elsevier; 2018. p. 191–205.
39. Tirumalasetty J, Grammer LC. Asthma, surgery, and general anesthesia: a review. J Asthma. 2006;43(4):251–4.
40. Leary D, Svenningsen S, Guo F, Bhatawadekar S, Parraga G, Maksym GN. Hyperpolarized 3He magnetic resonance imaging ventilation defects in asthma: relationship to airway mechanics. Physiologic reports. 2016;4:(7)e12761.
41. Svenningsen S, Kirby M, Starr D, Leary D, Wheatley A, Maksym GN, et al. Hyperpolarized (3) He and (129) Xe MRI: differences in asthma before bronchodilation. J Magnet Resonance Imaging. 2013;38(6):1521–30.
42. Aysola R, de Lange EE, Castro M, Altes TA. Demonstration of the heterogeneous distribution of asthma in the lungs using CT and hyperpolarized helium-3 MRI. J Magnet Resonance Imaging 2010;32(6):1379–1387.
43. Thomen RP, Sheshadri A, Quirk JD, Kozlowski J, Ellison HD, Szczesniak RD, et al. Regional ventilation changes in severe asthma after bronchial thermoplasty with (3)He MR imaging and CT. Radiology. 2015;274(1):250–9.
44. Bueno J, de Lange EE. Chapter 4 – persistence of ventilation defects in asthmatics A2 – Albert, Mitchell S. In: Hane FT, editor. Hyperpolarized and inert gas MRI. Boston: Academic Press; 2017. p. 61–70.
45. Cadman RV, Lemanske RF, Jr., Evans MD, Jackson DJ, Gern JE, Sorkness RL, et al. Pulmonary 3He magnetic resonance imaging of childhood asthma. J Allergy Clin Immunol. 2013;131(2):369–76.e1–5.
46. Witt CA, Sheshadri A, Carlstrom L, Tarsi J, Kozlowski J, Wilson B, et al. Longitudinal changes in airway remodeling and air trapping in severe asthma. Acad Radiol. 2014;21(8):986–93.
47. Trivedi A, Hall C, Hoffman EA, Woods JC, Gierada DS, Castro M. Using imaging as a biomarker for asthma. J Allergy Clin Immunol. 2017;139(1):1–10.

43 Endoscopic Repair of Tracheoesophageal Fistula

R. Paul Boesch

Background

Tracheoesophageal fistulas (TEF) can be congenital, acquired, or recurrent. They are rare, with the incidence of congenital fistulas reported to be 1 in 3500–4300 live births [1, 2]. Congenital fistulas are most often diagnosed at birth with the inability to feed orally due to esophageal atresia with a proximal blind-ended pouch as the most commonly presenting type [2]. Approximately one half of congenital TEF present with other anomalies such as VACTERL association (vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities), CHARGE syndrome (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities), or congenital heart or genitourinary defects. H-type TEF are usually diagnosed in the first few years of life but sometimes not until late childhood or adulthood, as they present with chronic not-specific symptoms such as chronic cough, congestion, wheezing, dysphagia, and recurrent respiratory infection [3–5]. Although congenital and recurrent TEF can be identified on esophagram, there is a high false-negative rate. The gold standard for identification is direct visualization with bronchoscopy and esophagoscopy (Fig. 43.1). Initial repair via thoracotomy or thorascopy is the typical approach. This can be accomplished by ligation, ligation and division, or full excision with the repair of tracheal and esophageal walls [6]. For some large or complex TEF, slide tracheoplasty has also been described [7]. Fistula localization can be difficult with open repair and can be aided by bronchoscopic placement of a guidewire or catheter for tactile identification or transillumination with a flexible bronchoscope. Success rates are high for closure of congenital TEF with very low perioperative mortality. Fistula recurrence after primary repair is reported to be 3.3–15%, with an average of 10% [8–10]. Management of recurrent fistulas is much more difficult and associated with a much higher rate of morbidity and a re-recurrence rate of 10–22% [11, 12]. For this reason, endoscopic repair of TEF has been seen as a potentially attractive option with the first report as far back as 1974 [13].

Approaches to Endoscopic Repair

Twenty-six studies reported between 1974 and 2017 describe techniques, success, complications, and follow-up of variable approaches to endoscopic closure. The majority of patients included in these studies had recurrent TEF (rTEF) and a few with congenital H-type TEF (cTEF). In general, TEF treated via endoscopic methods tend to

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*, Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4_43

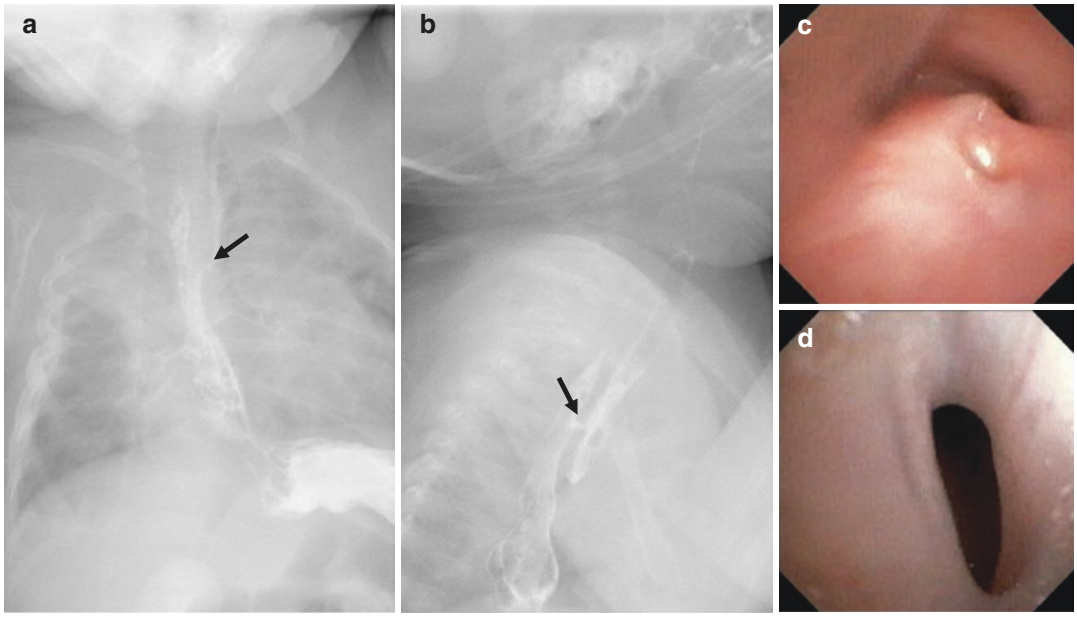

Fig. 43.1 Diagnosis of tracheoesophageal fistula (TEF). Large recurrent TEF identified within the repair of congenital type C TEF by esophagram (**a** + **b**, arrows) and by flexible bronchoscopy (**c** + **d**). With gentile pressure, 3.1 mm bronchoscope obtains eye-through-keyhole view but cannot pass through fistula, estimating size near 2 mm (**d**)

be small and non-patulous (to increase success rate) and recurrent (to avoid increased morbidity of open treatment). Closure of endoscopic fistula is best for fistula that are longer and <2 mm in diameter, but successful closure has been reported for fistula as wide as 6 mm [14]. The most common methods for endoscopic TEF obliteration include either de-epithelialization alone, sealant application alone, or a combination of both. Methods and materials used are variable and most reports are small case series.

De-epithelialization methods described include mechanical debridement, electrical diathermy, laser, or chemical. Mechanical debridement can be performed with a brush or rigid suction catheter [15]. Both potassium titanyl phosphate (KTP) and Nd:YAG have been reported as a method for laser de-epithelialization of the fistula tract, from the tracheal side as well as from the esophageal side [16–18]. By far the most commonly reported method for de-epithelialization is with electrical diathermy, also commonly referred to as electrocautery [19–27]. Monopolar electrodes, as are most often employed in urological procedures, are well-suited for this purpose. One such electrode, the Bugbee fulgurating diathermy electrode (ACMI Corp, South Borough, MA) comes in sizes down to 3F, which can be passed through a 1.2 mm operating channel of a flexible bronchoscope, and short and long lengths depending on use via a rigid or flexible bronchoscope. This electrode can also be used to probe a TEF pouch and evaluate for continuity with the esophagus (such as by passing and endoscope or flexible bronchoscope into the esophagus). Because the current from monopolar instruments passes through the patient, a grounding pad is required. Low wattage in coagulation mode is preferred (5–15 Watts) to limit thermal spread and injury to surrounding tissues. The catheter should be inserted into the fistula and short burst of cautery applied as the electrode is pulled back into the trachea. The goal is dessication and fulguration of all internal surfaces of the fistula tract and multiple passes may be required. The tissue should have a white appearance circumferentially (Fig. 43.2). Prolonged single application of cautery may result in tissue edema and necrosis, with slower healing and potentially less success. Therefore,

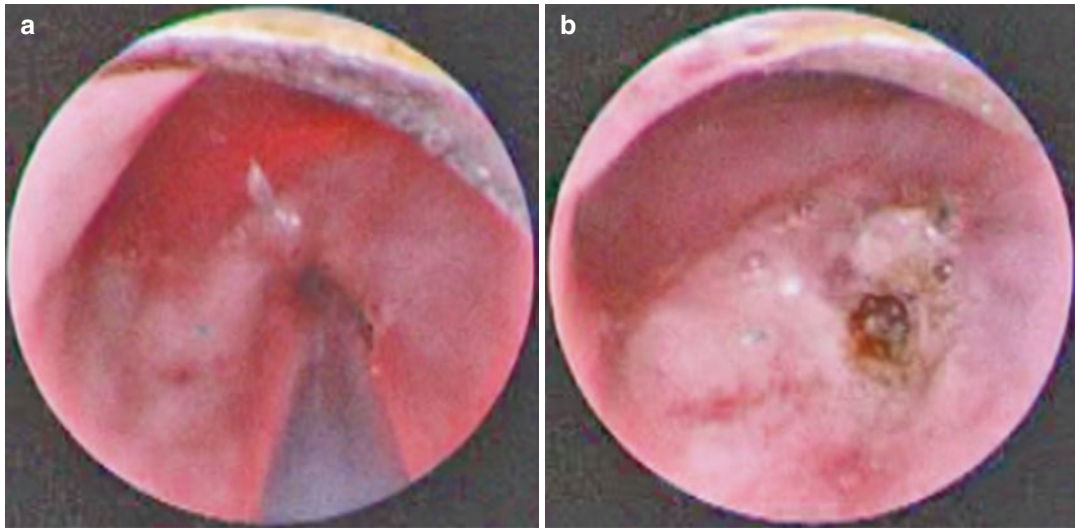

Fig. 43.2 Bugbee fulgurating diathermy electrode probing a recurrent tracheal esophageal fistula (**a**). Fistula following diathermy showing circumferential white, blanched mucosa (**b**)

multiple passes with short dwell times is preferred. Most authors do not report the use of additional diathermy from the esophageal side.

Lasers have also been employed for de-epithelialization but with lesser frequency [16–18]. The effectiveness of laser for endoscopic obliteration appears similar to other methods though this is based on only six reported patients across three studies. Rakoczy et al. reported successful closure of a fistula with KTP laser following three failed attempts with diathermy and fibrin glue [18]. Compared to diathermy, the use of laser is more costly and requires more complicated set-up and time.

Chemical methods include one report of polidocanol in one patient and two studies of 17 total patients utilizing 50% trichloroacetic acid (TCA) [28–30]. The method described for TCA generally requires a rigid bronchoscope to protect the laryngeal structures and trachea from contact with the acid. The bronchoscope should be positioned against the posterior wall, just at the opening of the fistula to ensure proper localized application of the TCA. Rotation of the bronchoscope such that the bevel is oriented into the fistula may also be helpful. Very small cotton (2 mm) are then soaked in the acid and grasped by rigid forceps. Three passes are then made, brushing the lumen of the fistula for 30 seconds.

Any de-epithelization procedure can be repeated at monthly or greater intervals until closure is achieved or decision is made to convert to open repair. De-epithelialization by any method may be utilized alone or in combination with the application of a tissue sealant, though the addition of a sealant has not been described for TCA.

Various sealant agents have been reported for use in endoscopic TEF repair, the first being histoacryl (*n*-butyl-z-cyanoacrylate) by Gdanietz et al. in 1974 [13]. Since this initial report, there have been five additional, three with histoacryl alone, and two in combination with de-epithelialization [14, 23, 28, 31, 32]. Direct instillation through an angiographic catheter is described [23]. Eventual closure rate is similar between those undergoing de-epithelialization first, but there were 0 of 7 closed on the first application with histoacryl alone whereas 5 of 10 closed the first time when combined with diathermy [13, 14, 23, 28, 31, 32].

Fibrin glue is a combination of fibrin, sealer protein, and fibrinolytic inhibitor (aprotinin) that can be injected directly into the lumen of the fistula to induce and inflammatory response

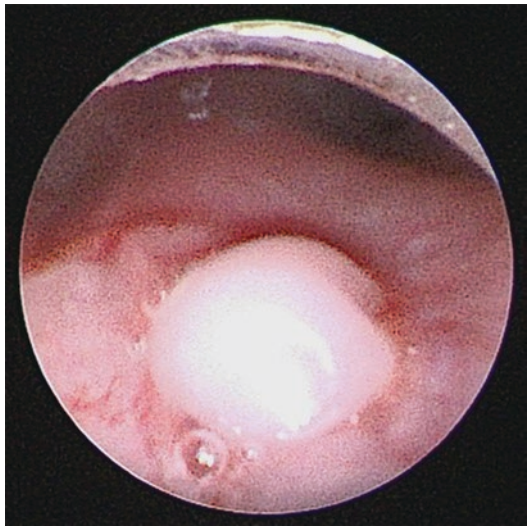

Fig. 43.3 Fibrin glue sealant placed in previously cauterized recurrent tracheoesophageal fistula

with granuloma formation and epithelialization. It is commonly used in thoracic surgery and has a good safety profile. Application results in the formation of an elastic clot within the lumen that is completely resorbed in 10–14 days, though shrinkage and expulsion from the fistula may occur in only 2–3 days (Fig. 43.3). Fibrin glue is a commonly used agent, either alone or in combination with de-epithelialization. Tisseel (Baxter Healthcare Corp, Westlake Village, CA) is a prepackaged fibrin glue that can be directly instilled through a stiff dual-lumen catheter such that the fibrinogen and fibrin do not come into contact and react until they are within the lumen of the fistula. This catheter can be guided through a rigid bronchoscope or alongside a rigid telescope, but not advanced through a flexible bronchoscope. Following the placement of the fibrin glue, it is prudent to remove any material that has spilled over into the trachea. Twelve case series document the use and outcomes of fibrin glue with generally good success [15, 18, 20, 22, 24, 25, 27, 33–37]. Whether used in isolation or with de-epithelialization, there was eventual closure in 88.9% from pooled data across studies (27 total patients). Contrary to this, Gutierrez, et al. had better outcomes when applied with diathermy [24]. Across these studies, the addition of de-epithelialization did increase the rate of closure after the first procedure from 11.1% to 38.9%.

Tracheal Diverticula

Residual tracheal diverticula are common after primary TEF repair though they are typically small and shallow and rarely symptomatic. Distal TEF typically leave small pouches as surgical exposure of distal TEF is excellent, facilitating ligation very close to the tracheal wall. Proximal pouches are both more likely to be larger and to be symptomatic. These can present a variety of ways [38]. The first is with recurrent lower respiratory tract infections from secretion pooling in a large pouch. The level of the pouch may also result in a focal level of severe tracheomalacia, with the lip itself creating a narrow-most choke point for collapse, resulting in airway obstruction and/or recurrent respiratory infections from poor airway clearance. Lastly, they may complicate tracheostomy placement or endotracheal intubation with the tube inadvertently cannulating the pouch resulting in severe acute obstruction and inability to ventilate. The primary method of management involves division of the party wall between the diverticulum and the trachea. This may be accomplished via CO_2 laser ablation, division with laryngeal scissors, fulguration with Bugbee electrode, or with electrocautery forceps [38–40]. As with TEF repair, the use of laser requires additional cost, time, and expertise compared to other methods. Electrocautery forceps, such as Clickline (Karl Storz Endoscopy, Culver City, CA) or LigaSure (ValleyLab, Tyco Healthcare Group, Boulder, CO), provide quick access and cutting with hemostasis which improves visualization [38, 39]. This author has also had good experience with cauterization with a Bugbee electrode via a flexible bronchoscope in children with poor exposure by rigid instruments.

Success with Endoscopic Repair

Generally, endoscopic repair of TEF are quick procedures, lasting as little as 30 minutes. They are associated with low mortality with only one reported patient death across all reported series, which was attributed to severe underlying disease [23]. There is also low reported morbidity with postoperative respiratory distress occurring in 5%, one reported episode of pneumonia, and one aspirated fibrin glue plug that resulted in aspiration and required retrieval [20, 30, 41].

Endoscopic TEF repair has a high rate of successful closure (>80%), regardless of method. The likelihood of closure after only one procedure, however, is much lower and more variable by approach, favoring de-epithelialization with sealant over sealant alone (Table 43.1). De-epithelialization with TCA has the highest total success rate at 100% (based on 17 patients) but has a lower rate of success after one application (35.3%). Diathermy alone has a success rate of only 28.6%, but this is based on only seven combined patients. It is important to remember that this outcome data comes from pooling results from multiple small case series over 45 years, which limits true comparative evaluation of methods. Regardless of approach, patient selection is important, favoring thinner and longer fistula for successful closure.

Endoscopic repair is attractive for recurrent TEF largely over its much lower morbidity as compared to open repair, but this benefit is tempered by the common need for repeated procedures to achieve closure. Success after the first procedure is only ~34% from the review of all methods. This results in multiple anesthetic exposures, separated by a month, or months, which may delay definitive closure. On average, 2.1 procedures are required to achieve complete closure, with a range of 1–6 [41]. Many practitioners will attempt 2 or 3 endoscopic repairs before reverting to open repair.

There has also been concern over long-term durability of endoscopic TEF closure. Willetts et al. evaluated this via postal survey of 11 institutions who reported back follow-up of endoscopic appearance, esophagoscopy, and/or symptoms [35]. They found, with a median follow-up of 107 months, a long-term success rate of only 54.5%, with all recurrences occurring in the first year. This compares poorly to the 10–22% recurrence rate from open re-repair [11, 12]. However, subsequent authors have reported durable results over several years of follow-up, up to 9 years [15, 23, 25, 29, 30]. Lelong et al. reported follow-up of 14 patients after TCA closure for 12–72 months, with only one patient <2 years, without any recurrence [30]. While

Table 43.1 Comparison of results of endoscopic tracheoesophageal fistula repair, across all methods, from pooled data

Method	Success/ total patients	% success	Studies [reference]
Total success – all methods	63/73	86.3%	26 studies
1st treatment success – all methods	25/73	34.2%	
Total success – all with de-epithelialization	49/56	87.5%	16 studies
1st treatment success – all with de-epithelialization	21/56	37.5%	[15–30]
Total success – all with sealant	41/46	89.1%	20 studies
1st treatment success – all with sealant	19/46	41.3%	[13, 15, 18, 20, 22–28, 31–37]
Total success – de-epithelialization + sealant	26/29	89.7%	10 studies
1st treatment success – de-epithelialization + sealant	14/29	48.3%	[15, 18, 20, 22–28]
Total success – De-epithelialization alone	23/27	85.2%	6 studies
1st treatment success – De-epithelialization alone	9/27	33.3%	[16, 17, 19, 21, 29, 30]
Total success – sealant alone	14/16	87.5%	10 studies
1st treatment success – sealant alone	4/16	25%	[13, 14, 31–37]

persistence of fistula after a first attempt of endoscopic closure is very common, the true incidence of late recurrence after successful closure may not be known.

Summary

Endoscopic repair of recurrent and congenital H-type TEF is relatively straightforward with short operative times and low morbidity and mortality. This is of particular advantage in recurrent TEF where repeat open procedure carries much higher risk and still a high re-recurrence rate. As in any surgical procedure, patient selection is essential and endoscopic approaches are best for longer and narrower fistula where coaptation of tissue is more likely to occur. It can easily be done in fistula of 3–4 mm diameter. Success of first-time and eventual closure may be highest with both de-epithelialization and sealant, though differences between methods are small and lack certainty based on small numbers, with no directly comparative evidence. The higher success rate reported with TCA alone needs substantiation with more time and experience. The need for repeated procedures results in greater anesthetic exposures and may delay time to complete closure. The long-term recurrence after the documentation of complete closure is largely unknown. Overall, endoscopic repair of TEF is a useful procedure for the pediatric otolaryngologist or pediatric pulmonologist comfortable with rigid bronchoscopy.

References

1. Lupo PJ, Isenburg JL, Salemi JL, Mai CT, Liberman RF, Canfield MA, Copeland G, Haight S, Harpavat S, Hoyt AT, Moore CA, Nembhard WN, Nguyen HN, Rutkowski RE, Steele A, Alverson CJ, Stallings EB, Kirby RS, and the National Birth Defects Prevention Network. Population-based birth defects data in the United States, 2010–2014. A focus on gastrointestinal defects. Birth Defects Res. 2017;109(18):1504.
2. Shaw-Smith C. Oesophageal atresia, tracheaoesophageal fistula, and the VACTERL association: review of genetics and epidemiology. J Med Genet. 2006;43:545–54.
3. Cassina M, Ruol M, Pertile R, Midrio P, Piffer S, Vicenzi V, Saugo M, Stocco CF, Gamba P, Clementi M. Prevalence, characteristics, and survival of children with esophageal atresia: a 32-year population-based study including 1,417,724 consecutive newborns. Birth Defects Res A Clin Mol Teratol. 2016;106(7):542–8.
4. Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. Chest. 2004;126:915–25.
5. DeBoer EM, Prager JD, Ruiz AG, Jensen EL, Deterding RR, Friedlander JA, et al. Multidisciplinary care of children with repaired esophageal atresia and tracheoesophageal fistula. Pediatr Pulmonol. 2015;51:576–81.
6. Daniel SJ, Smith MM. Tracheoesophageal fistula: open versus endoscopic repair. Curr Opin Otolaryngol Head Neck Surg. 2016;24:510–5.
7. Provenzano MJ, Rutter MJ, von Allmen D, Manning PB, Boesch RP, Putnam PE, et al. Slide tracheoplasty for the treatment of tracheoesophageal fistulas. J Pediatr Surg. 2014;49(6):910–4.
8. Tsai JY, Berkery L, Wesson DE, Redo SF, Spigland NA. Esophageal atresia and tracheoesophageal fistula: surgical experience over two decades. Ann Thorac Surg. 1997;64(3):778–83.
9. Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. Chest. 2004;126:915–25.
10. Allin B, Knight M, Johnson P, Burge D. Outcomes at one-year post anastomosis from a national cohort of infants with oesophageal atresia. PLoS One. 2014;9:e106149.
11. Spitz L, Kelly E, Brereton RJ. Esophageal atresia: five year experience with 148 cases. J Pediatr Surg. 1987;22:103–8.
12. Myers NA, Beasley SW, Auldist AW. Secondary esophageal surgery following repair of esophageal atresia with distal tracheoesophageal fistula. J Pediatr Surg. 1990;25:773–7.
13. Gdanietz K, Wiesner B, Krause I, Mau H, Jung FJ. Tissue-adhesive for sealing of oesophageal fisula in children (author's transl). Z Erkr Atmungsorgane. 1974;141:46–50.
14. Vandenplas Y. Endoscopic closure of recurrent tracheo-oesophageal fistula. Lancet. 1991;338:1147.
15. Meier JD, Sulman CG, Almond PS, Holinger LD. Endoscopic management of recurrent tracheoesophageal fistula: a review of techniques and results. Int J Pedatr Otorhinolaryngol. 2007;71:691–7.
16. Schmittenbecher SS, Mantel K, Hofmann U, Berlien HP. Treatment of congenital tracheoesophageal fistula by endoscopic laser coagulation: preliminary report of three cases. J Pediatr Surg. 1992;27:26–8.
17. Bhatnagar V, Lal R, Sriniwas M, Agarwala S, Mitra DK. Endoscopic treatment of tracheoesophageal fistula using electrocautery and the Nd:YAG laser. J Pediatr Surg. 1999;34:464–7.
18. Rakoczy G, Brown B, Barman D, Howell T, Shabani A, Khalil B, et al. KTP laser: an important tool in

refractory recurrent trachea-esophageal fistula in children. Int J Pediatr Otorhinolaryngol. 2010;74:326–7.
19. Rangecroft L, Bush GH, Lister J, Irving IM. Endoscopic diathermy obliteration of recurrent tracheoesophageal fistulae. J Pediatr Surg. 1984;19:41–3.
20. Wiseman NE. Endoscopic closure of recurrent tracheoesophageal fistula using Tisseal. J Pediatr Surg. 1995;30:1236–7.
21. Holland AJ, Ford WD, Guerin RL. Median sternotomy and use of a pedicled sternocleidomastoid muscle flap in the management of recurrent tracheoesophageal fistula. J Pediatr Surg. 1998;33:657–9.
22. McGahren ED, Rodgers BM. Bronchoscopic obliteration of recurrent tracheoesophageal fistula in an infant. Endosurg Inno Tech. 2001;5:37–42.
23. Tzifa KT, Maxwell EL, Chait P, James AL, Forte V, Ein SH, Friedberg J. Endoscopic treatment of congenital H-type and recurrent tracheoesophageal fistula with electrocautery and histoacryl glue. Int J Pediatr Otorhinolaryngol. 2006;70:925–30.
24. Gutiérrez San Roman C, Barrios JE, Lluna J, Ibañez V, Hernández E, Ayuso L, et al. Long-term assessment of of the treatment of recurrent tracheoesophageal fistula with fibrin glue associated with diathermy. J Pediatr Surg. 2006;41:1870–3.
25. Richter GT, Rykman F, Brown RL, Rutter MJ. Endoscopic management of recurrent tracheoesophageal fistula. J Pediatr Surg. 2008;43:238–45.
26. Gregory S, Chun RH, Parakininkas D, Amos L, Fons R, Lerner DG, et al. Endoscopic esophageal and tracheal cauterization for closure of recurrent tracheoesophageal fistula: a case report and review of the literature. Int J Pediatr Otorhinolaryngol. 2017;98:158–61.
27. Nazir Z, Khan MAM, Qamar J. Recurrent and acquired tracheoesophageal fistulae (TEF)-minimally invasive management. J Pediatr Surg. 2017;52:16788–90.
28. Al-Sammari AY, Jessen K, Haque K. Endoscopic obliteration of a recurrent tracheoesophageal fistula. J Pediatr Surg. 1987;22:993.
29. Sung MW, Chang H, Hah JH, Kim KH. Endoscopic management of recurrent tracheoesophageal fistula with trichloroacetic acid chemocauterization: a preliminary report. J Pediatr Surg. 2008;43:2124–7.
30. Lelonge Y, Varlet F, Varela P, Saitúa F, Fourcade L, Gutierrez R, et al. Chemocauterization with trichloroacetic acid in congenital and recurrent tracheoesophageal fistula: a minimally invasive treatment. Surg Endosc. 2016;30:1662–6.
31. Pompino HJ. Endoscopic closure of tracheaoesophageal fistulae. Z Kinderchir. 1979;17:137–8.
32. Waag KL, Joppich I, Manegold BC, et al. Endoscopic closure of trachea-esophageal fistulae. Z Kinderchir. 1979;27:93–6.
33. Daniel P, Martin S, Grahl KO. Problem of endoscopic gluing on an esophagotracheal fistula recurrence following surgery for esophageal atresia using tissue adhesives. Zentralbl Chir. 1980;105:1522–4.
34. Gutierrez C, Barrios JE, Lluna J, Vila JJ, Garcia-Sala C, Roca A, et al. Recurrent tracheoesophageal fistula treated with fibrin glue. J Pediatr Surg. 1994;29:1567–9.
35. Willetts IE, Dudley NE, Tam PK. Endoscopic treatment of recurrent trachea-oesophageal fistulae: long-term results. Pediatr Surg Int. 1998;13:256–8.
36. Hoelzer DJ, Luft JD. Successful long-term endoscopic closure of a recurrent tracheoesophageal fistula with fibrin glue in a child. Int J Pediatr Otorhinolaryngol. 1999;48:259–63.
37. Lopes MF, Pires J, Nogueria Brandão A, Reis A, Morais Leitão L. Endoscopic obliteration of a recurrent tracheoesophageal fistula with enbucrilate and polidocanol in a child. Surg Endosc. 2003;17:657.
38. Johnson LB, Cotton RT, Rutter MJ. Management of symptomatic tracheal pouches. Int J Pediatr Otorhinolaryngol. 2007;71:527–31.
39. Cheng ATL, Gazali N. Acquired tracheal diverticulum following repair of trachea-oesophageal fistula: endoscopic management. Int J Pediatr Otorhinolaryngol. 2008;72:1269–74.
40. Shah AR, Lazar E, Atlas AB. Tracheal diverticula after tracheoesophageal fistula repair: case series and review of the literature. J Pediatr Surg. 2009;44:2107–11.
41. Aworanti O, Awadalla S. Management of recurrent tracheoesophageal fistulas: a systematic review. Eur J Pediatr Surg. 2014;24:365–75.

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S. Goldfarb, J. Piccione (eds.), *Diagnostic and Interventional Bronchoscopy in Children*,
Respiratory Medicine, https://doi.org/10.1007/978-3-030-54924-4

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