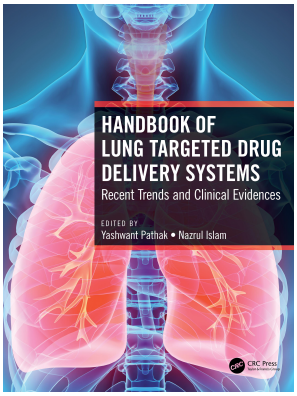

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

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Effect of Aerosol Devices and Administration Techniques on Drug Delivery in a Simulated Spontaneously Breathing Pediatric Tracheostomy Model

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12.1 Introduction

The effectiveness of aerosol drug delivery in pediatric patients is contingent on several factors: the anatomy of the developing lungs, the physiology of the disease, the pharmacology of the drug being dispensed, and the mode and technique of drug administration. From this, it is clear that optimization of aerosol drug delivery requires clinical understanding, as well as knowledge of proper devices and administration techniques. This chapter focuses on aerosol drug delivery devices and modes of administration in pediatric patients, supported by recent research using simulated, spontaneously breathing pediatric tracheostomy models. Spontaneously breathing tracheostomy models allow researchers to mimic the respiratory patterns of pediatric patients. For most of the research discussed, spontaneous breathing was simulated using tracheostomy tubes, a training lung with a lift bar, and a connected ventilator. The ventilator cycles, filling up the trigger chamber, and the lift bar simulates inspiration by lifting the test chamber. Expiration is passive and resistance levels can be set. Breathing parameters varied between studies called upon during this chapter. In general, when mimicking pediatric patients, studies had an average respiratory rate of 25 breaths/min, tidal volume of 150 ml, inspiratory time of 0.8 seconds, and peak inspiratory flow of 20 l/min (1). From this, recommendations on delivery will be provided, with special considerations that should be taken for pediatric patients.

There are many potential benefits of using inhalation drug therapy rather than oral or intravenous. Aerosol delivery is less invasive, smaller doses can be used to achieve the same therapeutic effect, and the onset of the effect can be more rapid. In addition, delivery into the lungs exposes the drug to a rich supply of blood. Lung delivery avoids an initial first pass through the liver or stomach, potentially avoiding adverse reactions or metabolic inactivation of drug factors. Not only is aerosol inhalation the predominant portal of entry of drugs for pulmonary diseases, but lung delivery can also be considered to treat some systematic issues (2). Optimizing the delivery of aerosol drugs will contribute to long-term artificial airway treatments in patients with tracheostomies as well as the acute and chronic treatment of respiratory diseases in spontaneously breathing children.

12.2 Anatomical and Physiological Factors

Initially, aerosol drugs can only reach regions that encounter gas flow. This means that the anatomy and physiology of the lungs have a strong effect on the delivery of an inhaled drug. The branching of the respiratory tract increases the surface area available for absorption of the drug, from the air into pulmonary epithelium. This enhances the delivery efficiency of drugs inhaled into the pharynx, larynx, bronchi, bronchioles, alveoli, and finally capillaries, which then transport the drug to its target tissue.

Deposition is when the gaseous drug converts into a solid form. The goal of treatment is for this solid to then be absorbed into the respiratory tissue. The specific region that deposition occurs in can affect the absorption and thus therapeutic effectiveness of the treatment. Deposition can occur in the epithelium of the mouth, nose, pharynx, trachea, bronchi, and alveoli. When drugs are deposited in the upper respiratory tract much is lost or exhaled and only a fraction of drug will reach target tissue. Drug delivery devices are constantly being innovated to optimize this by depositing drugs further down the respiratory tract. Pressure, temperature, and moisture can affect drug deposition by directly modifying the active pharmaceutical ingredients or the ability of the respiratory cells to absorb the dissolved drug (3). This means that the type of device and drug chosen will greatly influence the deposition rate that occurs in target tissue. Factors that affect drug deposition must be considered in order to optimize delivery of the drug. Another factor that will affect drug deposition is the physiology of breathing.

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Measurement of the movement of incoming air or administered drugs is termed *flow rate*. Peak inspiratory flow rate can be used to measure the deposition abilities of certain devices, such as dry powder inhalers and pressurized metered-dose inhalers. Air flow resistance is the force that opposes the movement of air in or out of the lungs. The work of breathing is the work a patient must exert to breathe spontaneously. In other words, the physiologic force of air needed to oppose the resistance of air flow. When choosing an aerosol drug delivery device, consider one that decreases resistance and thus imposed work of breathing, while also promoting high levels of deposition into the desired respiratory tissue.

Physiologic work can be measured using esophageal balloons and a Campbell diagram to integrate work from the balloon's pressure measurements (4). The imposed work of breathing is an important measurement when dealing with inhalation drug therapy because it describes the work a patient must exert to breathe spontaneously through a machine, such as an inhaler or ventilator. This is the work needed to oppose the resistance of the respiratory apparatus itself. The total work of breathing is the summation of physiologic and imposed work. Imposed work exceeding physiologic work may lead to an increase in respiratory muscle load, which can lead to muscle fatigue, especially in pediatric patients.

The issue of muscle fatigue can be avoided by minimization and monitoring of imposed work. Transducers, polygraph recorders, X-Y plotters, and other technology can be used to measure imposed work, but operating these devices requires training (4). This is why computerized pediatric respiratory monitors, such as the CP-100 Pediatric, Bicore Monitoring Systems, are used. Validation studies have found these devices to accurately measure imposed work, tidal volume, flow rate, and tracheal airway pressure during spontaneous ventilation. The device that is chosen needs to be set in order to support ventilation and keep imposed work as close to zero as possible. Some ways to decrease imposed load include larger diameter endotracheal tubes, humidifiers, positive airway pressures, and expiratory valves (4).

12.3 Devices

Nasal sprays are a simple way to deliver drugs to the upper respiratory system or sinuses (5). Although they are simple and can be effective for some drugs, these devices are restricted as to the formulations they can deliver. Antibiotics, mucolytics, liposomal, and recombinant drugs are difficult to safely and efficiently delivery with inhalers or sprays. Examples of respiratory devices for drug delivery are shown in Table 12.1.

Another common therapeutic aerosol delivery system is the inhaler. Different types of inhalers include pressurized metered-dose, dry powder, and soft mist. Pressurized metered-dose inhalers (pMDI) administer the drug through a mouthpiece, using a pressurized propellant. pMDI are compact, quiet, fast, and inexpensive. The drug itself is typically sealed and protected from the environment and the dosing is easily reproducible. That being said, the types of drugs pMDI can deliver are more limited than other delivery modalities. There is also a high level of oropharynx drug deposition when using this technique, which is sometimes associated with less efficient absorption. Finally, it may be difficult to synchronize patient breathing with the device, especially with very young patients. Using spacers and valve holding chambers can mitigate these downfalls. When using a pMDI, patients can either use an open-mouth technique, closed-mouth technique, or a spacer. A spacer captures aerosol to decrease oropharynx deposition. The valve holding chamber manually synchronizes actuation of the drug with the patient's inhalation (1).

Dry-powder inhalers (DPI) deliver drug in a powdered form, typically paired with an actuated dosing system. DPI are portable and breath actuated, meaning they do not use propellants like pMDI, but administer medication using the patient's inspiratory flow. DPI are easy to use and do not require synchronization of breathing and thus have no need for spacers. On the other hand, DPI require more force and effort from the patient which can lead to muscle fatigue, especially in younger patients. The harder and deeper patients are able to inhale, the more medication that can be delivered. This means that dosing can be inconsistent, and the drug is susceptible to environmental effects like humidity and temperature (9).

The final type of inhaler this chapter will discuss is soft mist inhalers (SMI). SMI create clouds of medication with a higher concentration of particles than MDI or DPI. No propellant is needed, and lower doses can be used because the mist is produced at a slower speed, reducing oropharynx deposition. Some research has linked SMI administration of tiotropium with a higher risk of death in people with chronic obstructive pulmonary disease (COPD) (23).

The development of nebulizers revolutionized the delivery of aerosol drugs by allowing quick and efficient transformation of liquid drug into an inhalant. Small-volume nebulizers (SVN) are typically categorized as jet, ultrasonic, or mesh. SVN are powered by compressed air, oxygen, a compressor, and an electricity source to generate aerosol from a liquid drug (9).

Jet nebulizers (JN) are a common choice for the treatment of many pulmonary diseases but can be inconvenient for patients because they are not optimally portable and require a power source to function. JN use compressed gas to shoot a drug-containing aqueous solution into a stream of droplets via a mouthpiece or mask. This makes it an option for children of any age group and cooperation level, because there is no advanced technique required to use the device. Many different types of drugs can be delivered with JN, at considerably high doses. On the other hand, JN are sometimes avoided because they can be bulky, susceptible to contamination, and can be wasteful due to low delivery efficiency (1).

Ultrasonic nebulizers are more discreet and efficient, but are restricted as to what kind of drugs can be used because the heat produced during administration can denature protein-based drugs. Mesh nebulizers use micropump technology and low-frequency waves that avoid this heat and are thus able to deliver more sensitive, protein-containing suspensions (6). Vibrating mesh nebulizers (VMN) contain a plate that vibrates to generate aerosol particles. VMN must be handled with care and cleaned regularly to avoid blockage. VMN are discreet, portable, and have fast nebulizer times, meaning more effectiveness at converting liquid medicine into the fine spray necessary for absorption (1).

TABLE 12.1

Respiratory Devices for Drug Delivery

Device	Typical Appearance	Description
Pressurized metered dose inhaler (pMDI)	A handheld, portable device with a mouthpiece on the bottom and a formulation container on the top. The mouthpiece is covered by a lid that must be removed prior to use.	Administers the drug through a mouthpiece, using a pressurized propellant. pMDI are quiet, fast, and inexpensive. Sometimes known as a "puffer".
Soft mist inhaler (SMI)	Similar to the pMDI, the SMI has a mouthpiece, but it may be on the top or bottom. On the opposite end of the mouthpiece is a drug-containing cartridge. There is a dose release button and capillary tube with a spring in order to deliver formulations.	Create clouds of medication with a higher concentration of particles than MDI or DPI. No propellant is needed and lower doses can be used.
Dry-powder inhaler (DPI)	DPI come in several different designs, but typically are either round or straight with a capped mouthpiece, protective screen leading to a capsule chamber on the inside, and button for aerosol release. DPI come in single and multi-dose designs.	Delivers drug in a powdered form, typically paired with an actuated dosing system. DPI do not use propellants like pMDI, but administer medication using the patient's inspiratory flow.
Jet nebulizer (JN)	JN come with a mouthpiece or mask, connected to a drug-containing chamber, attached to a tube, which is connected to and powered by an air compressor.	Uses compressed gas to shoot a drug-containing aqueous solution into a stream of droplets.
Ultrasonic nebulizer	These nebulizers are smaller and more portable than the JN. Ultrasonic nebulizers also use mouthpieces or masks, but instead of tubing they are directly connected to the power source and formulation chamber.	Discreet and efficient, but are restricted in what kind of drug can be used because the heat produced during administration can denature protein-based drugs.
Vibrating mesh nebulizer (VMN)	VMN visually resemble ultrasonic mesh nebulizers but contain a membrane with many small holes on top of the liquid reservoir to disperse the formulation droplets.	Uses micropump technology and low-frequency waves that avoid heat and are thus able to deliver more sensitive, protein-containing suspensions.
Breath-enhanced nebulizer (BEN)	BEN have a chamber with a mouthpiece and liquid formulation container. This chamber is connected to tubing which connects to a power source.	Continues to deliver aerosol during exhalation as well as inhalation.
Breath-actuated nebulizer (BAN)	BAN look similar to BEN, except BAN contain a vent with a valve to allow air flow upon inspiration, but not expiration.	Delivers medication during inhalation only.

Breath-actuated nebulizers are part of a new, potentially more efficient generation of jet nebulizers that expel medication only during inspiration (7). The difference between breath-enhanced and breath-actuated nebulizers is that breath-actuated delivers medication during inhalation and breath-enhanced continues to deliver aerosol during exhalation as well. The administration of medication during exhalation can result in waste, because the patient is not inhaling the drug into respiratory tissue that the drug can optimally be deposited and absorbed into. A 2014 study using adult breathing models found that breath-actuated nebulizers delivered a more consistent dose, which allowed more confidence in titrating to lower effective doses. The same study also found that there was a reduced risk of under-dosing during disease progression with breath-actuated nebulizers (8,9).

VMN deliver higher inhaled mass percentage in adult models, and jet nebulizers (JN) deliver a lesser mass percentage in pediatric models (1). One study comparing JN, breath-enhanced nebulizers (BEN), breath-actuated nebulizers (BAN), manually triggered nebulizers (MTN), and vibrating mesh nebulizers (VMN) found that the VMN delivered the greatest inhaled drug dose (35.5%) and lowest residual dose (2.8%), and the JN and BENs delivering the lowest inhaled dose (15.0% and 17.7% respectively) and highest residual (62.3% and 66.2%). MTN and BAN had the lowest exhaled doses (1.7% and 2.7%), JN had the highest exhaled dose (15%), and VMNs resulted in relatively high exhaled dose as well (11.1%). This study was done using an in vitro and ex vivo adult model, so the lack of pediatric considerations in this data must also be noted (10).

As previously mentioned, humidification and temperature are two major factors affecting deposition and therefore absorption of the drug. Normally, the upper airway (mouth, pharynx, larynx) contributes moisture. This is bypassed in the long-term aerosol drug delivery in patients with tracheostomies. Special considerations, such as combining nebulizer use with humidification therapy, are considered for these patients. Three major types of humidification devices are typically used: heated, unheated, and heat-and-moisture exchangers (HME). A 2016 study on aerosol drug delivery and humidification therapy found that unheated humidifiers provided for more efficient drug delivery than heated, but that HME demonstrated the most efficiency. Specifically, the best drug delivery was seen in HME with passive exhaled humidification. This study also compared MTN and JN, finding MTN more effective (11).

12.4 Techniques

There is variation in the performance and convenience of the different drug delivery devices, depending on the patient and drug. Patients with artificial airways, like tracheostomies and endotracheal tubes, often require the administration of aerosol drugs. This may have an effect on drug deposition, and minimization of absorption barriers requires additional considerations.

When using a jet nebulizer, a T-connector and tracheostomy collar can be used. One study comparing the albuterol delivery of different types of nebulizers with a spontaneously breathing pediatric tracheotomy model found that using a jet nebulizer with a T-piece and resuscitation bag resulted in higher deposition than without. Other studies have shown T-pieces are more efficient than tracheostomy masks (1).

Aerosol drugs can be administered assisted or unassisted. In other words, via a manual resuscitation bag or directly. A study by Berlinski (12) showed that using a manual resuscitation bag and T-piece with a tracheostomy tube results in the highest inhaled dose. They compared albuterol delivery with a JN alone, with a corrugated tube, and with a corrugated tube and resuscitation bag. The study also compared T-pieces versus tracheostomy masks. The highest drug delivery was found with JN in conjugation with resuscitation bags and T-pieces. Positioning of the T-piece may also result in more or less efficient deposition of drug, but more research on this is needed (12).

In another study, pMDI was found to be more efficient when the T-piece was placed proximal to the spacer. This study simulated the unassisted technique by connecting the T-piece of a nebulizer to another T-piece, which was connected to a tracheostomy tube (TT). Corrugated tubing was used to connect the T-pieces and a pMDI canister was placed into the nozzle inlet of the spacer, connecting it to the TT. The assisted set-up involved jet and vibrating nebulizers attached to 450 ml pediatric manual resuscitation bags via T-piece adapters and corrugated tubing. Inhaled mass percent of nominal and emitted dose was used to determine efficiency. Nominal dose is the amount of drug that is contained within the reservoir of the nebulizer. Emitted dose is the amount that actually leaves the nebulizer as aerosol (1).

Frequent and long-term administration of pMDIs directly into patients' tracheostomy is not recommended unless an AeroChamber is used, as well. Without the chamber addition, that method has been shown to lead to hemoptysis and granulation tissue formation in bronchi. It is possible to adapt a volumetric spacer to fit a pediatric tracheostomy tube by cutting the barrel of a standard bladder irrigation syringe and attaching it to the outflow end of the spacer and the tube (1).

A study comparing aerosol delivery with a soft mist inhaler paired with a non-electrostatic valved holding chamber and deadspace volume mask reported transnasal delivery was more efficient compared to nasal and oral modalities for 5- and 14-month-olds (12). Another study compared transnasal albuterol delivery between VMN and continuous-output JN for different breathing parameters, set to mimic 7-month and 5-year-old children for tidal volumes of 25, 50, and 155 ml. Breathing frequencies were set to 40, 30, and 25 breaths/min, respectively. Inspiratory to expiratory ratios (I:E) of 1:3 and 1:2 were used. This study found that lung doses were larger for both age groups simulated when the JN was used transnasally. Lung dose is the portion of the nominal dose that is actually delivered to lung tissue. The JN produced 0.51%, 1.05%, and 0.97% lung doses on average, when delivered transnasally with the 7-month old model. The JN reached 0.44% and 1.14% for 50 and 155 ml tidal volumes, respectively, for the 5-month old model. As with the 5-month old JN model, VMN was not able to produce a measurably significant lung dose with the 25 ml tidal volume. With VMN, the 7-month-old model recorded 0.13% and 0.87% lung dose for 50 and 155 ml, and the 5-month-old model reached only 0% and 0.42%. The same study also showed that using a tightly sealed loading masking increased JN delivery significantly at lower tidal volumes (12).

A cascade impactor is used to measure distributed particulate size, which is important in determining the effective diameter of the nozzle of an administration device. Researchers can use this technology to determine what route of administration is best for certain particulate sizes. In general, the smaller the particulate size, the higher the lung dose recorded. One study found that the nasal route reported a higher percentage of deposition for particles smaller than 5 μm (97% vs 90%) and between 1 and 3 μm (49% vs 38%) when compared to the oronasal route (12).

Tidal volume is the amount of air that is displaced during non-forced inhalation and exhalation. For children, this is between 5 and 8 ml/kg of their body weight (13). One study found that increasing tidal volume during inhalation resulted in decreased lung dose. The study used budesonide administered via a pMDI with an 9-month-old model. The same study also showed lung dose was significantly higher with hydrofluoroalkane beclomethasone compared to chlorofluorocarbon beclomethasone (12).

Placement and size of nasal cannulas have also been shown to have an effect on flow and subsequent delivery of aerosolized drug. The cannula is a thin tube used to administer medication from the reservoir to the mouthpiece for patient inhalation. A study compared inspired dose percentages between three typical cannula sizes: infant, pediatric, and adult. The study found that the smaller the cannula, the lower the inspired dose. The study also found that increasing the flow rate from 3 and 5 to 10 l/min significantly decreased inhaled dose to almost nothing. While size of the cannula cannot always be modified, flow rate can and should be considered (12).

12.5 Pathological Considerations

In general, it is important to consider a child's ability to dependably operate and consistently use their medical inhalation device. A simple, easily transportable design is ideal, but optimization of drug delivery must be considered as well. The intricacies of the child's specific disease, unique living environment, and mental capacity should be taken into consideration before prescribing a treatment. First- or secondhand tobacco smoke, pollutants, infection exposure, nutrition, and other lifestyle attributes may play a role in the prognosis of chronic respiratory diseases and should also direct the treatment planning.

Lung disease can be categorized as either obstructive or restrictive. Obstructive lung diseases like asthma, emphysema, COPD, and cystic fibrosis make it difficult for patients to exhale air from their lungs. Medications that reduce the inflammation and narrowing of the airways can be used to treat symptoms. Inhalation medications that reduce narrowing by relaxing the smooth muscle of the respiratory tract are known as bronchodilators and include albuterol, ipratropium, formoterol, salmeterol, and tiotropium. Medications that target inflammation of the airways are typically corticosteroids, e.g. beclomethasone (14).

Restrictive pulmonary diseases are caused by a reduced ability to expand the lungs, such as with interstitial lung disease, sarcoidosis, some neuromuscular diseases, and some cases of scoliosis. Stiffness of the lungs or chest wall, muscle weakness, and damaged nerves can cause these diseases. Medications vary with the central cause, but therapies often involve anti-inflammatories. Both obstructive and restrictive lung diseases are associated with shortness of breath upon exertion and coughing (14).

With children, one of the most common forms of obstructive lung disease is asthma. The condition is chronic and often manifests in childhood, with symptoms that range from mild to severe. When approaching the treatment of asthma, medications are either for short-term relief or control. Short-term relief medications are used to prevent or relieve the symptoms of an asthma attack and include short-acting beta-2 agonsits (SABA), corticosteroids, or short-acting anti-cholinergics. Albuterol, a SABA, is one of the most commonly prescribed rescue medications. The delivery of albuterol using nebulizers with high gas flow has been found to be inefficient by some studies (1). Control medications may also be prescribed to these patients, intended for daily intake to help prevent symptoms even when an asthma attack is not imminent. Control medications include corticosteroids, monoclonal antibodies, mast cell stabilizers, inhaled long-acting bronchodilators (LABAs), and subcutaneous immunotherapy (14).

Cystic fibrosis is an inherited disease with variable penetrance that leads to thickening of mucus. Individuals with this disease may have issues breathing and a higher susceptibility to pulmonary infection resulting from the defective clearance of respiratory mucus. The ability to deliver anti-microbials quickly and effectively is of utmost importance with these patients. *Pseudomonas aeruginosa* is a frequent infection with these patients and can be treated with aztreonam in children older than 7 and tobramycin in children older than 6 (15).

Mucolytics are sometimes used in patients with cystic fibrosis or others that have mucus hypersecretion and retention. This pathology can also result from ciliary disease or from mucus-producing tumors that cause over-proliferation of goblet cells and submucosal glands. Mucolytics are sometimes called mucoactive agents and degrade polymer gels to promote clearance of sputum and a decrease of mucus hypersecretion. Aerosolized N-acetylcysteine uses its free sulfhydryl group to hydrolyze disulfide bonds in mucin and other proteins. *N*-acetylcysteine is a commonly use mucolytic but has a couple of issues, such as being inactivated at the airway surface and pre-systemically metabolized, lowering the concentration absorbed. It is also associated with a foul odor and airway irritation. Peptide mucolytics like dornase alfa can degrade polymerized collections of DNA and actin that may form during prolonged airway inflammation. Dornase has only shown to be effective in treating cystic fibrosis patients. Bland aerosols and bicarbonate can be used to produce an effective cough, but this is by irritating airway tissue and thus is not recommended (16).

Expectorants or secretagogues trigger coughing and the clearance of mucus by increasing water concentration in the airway. One example is hyperosmolar 7% saline and mannitol, an inexpensive solution that has been shown effective in patients with cystic fibrosis. It works due to mannitol's ability to attract water and secretions into the airway, and can sometimes trigger bronchospasms. P2Y2 purinergic pathway agonists, like denufosol, can promote chloride transport through functional membrane channels, also helpful with patients with cystic fibrosis. The use of an epithelial sodium channel inhibitor like amiloride is not recommended because it has not been shown effective and has been connected with exacerbated lung function (16).

Hospital-acquired and ventilator-associated pneumonia can occur with pediatric patients who are already hospitalized, undergoing ventilation therapy, and contract a respiratory bacterial infection. Inhaled antibiotics are recommended for patients not responding to intravenous medication or with gram-negative bacilli, bacteria that are only susceptible to aminoglycosides or polymyxins. Food and Drug Administration (FDA)-approved and commercially available inhalation antibiotics for this form of pneumonia include aztreonam, tobramycin solution, and tobramycin powder (15).

Other common causes of respiratory infection in children include general lower respiratory infections, bronchiolitis, influenza, respiratory syncytial viruses, the common cold, croup, streptococcal pharyngitis (also known as strep throat), and viral pneumonia. Four FDA-approved antivirals include oseltamivir phosphate, zanamivir, peramivir, and baloxavir marboxil. Croup, strep, and many cases of lower respiratory infections are bacterial and are often only treated with antibiotic inhalation therapy for severe cases (17).

The lungs are one of the last organs to mature in developing children. One issue in premature babies may be a collapse of alveoli due to a lack of surfactant. Surfactant keeps the alveoli open, allowing for gas exchange to occur. Surfactant replacement therapy can be used to prevent respiratory distress in neonates, when paired with supplementation of oxygen or ventilation. Surfactant replacement is a mixture of phospholipids and proteins that coat the alveoli to reduce surface tension and prevent atelectasis. It can be given prophylactically or as a rescue treatment and has been shown to reduce infant mortality and respiratory morbidity. Surfactant treatment may also be considered with neonates suffering from severe meconium aspiration syndrome, pulmonary hemorrhage, or severe respiratory syncytial virus-induced failure (18).

Aerosolized drugs have also been manufactured to deliver gene and peptide therapies. There are several different mechanisms these drugs work by. Some inhaled agents of gene therapy contain nucleic acids that can block abnormal gene production. Inhalation gene therapies are currently being investigated to treat patients with lung cancer, *Mycobacterium tuberculosis* infection, alpha-1 antitrypsin deficiency, and cystic fibrosis. Other medications may contain peptides that can be delivered directly to lung tissues, in order to treat pulmonary disease such as asthma, sarcoidosis, pulmonary hypertension, and cystic fibrosis. Administration of peptide drugs that target systemic circulation, such as insulin and calcitonin, are also being considered for inhalation therapies. Viral vectors, plasmids, cationic molecules, and interfering RNAs are among some of the formulations used to deliver those categories of drugs (19).

Some children with hemodynamic or circulatory instability require treatments that increase cardiac output and vascular resistance. Systemic vasoactive medication taken orally or intravenously may have minimal selectiveness and therefore

cannot target pulmonary epithelium unless delivered via aerosol. If blood pressure issues persist after the use of fluid resuscitation, inhalation therapy may be considered. Vasopressor drugs may help treat these patients by increasing contractility and heart rate or vasoconstricting peripherally. Vasodilators can also help by controlling vascular resistance. For instance, the drugs typically used to treat pediatric pulmonary hypertension target pulmonary vascular resistance and can result in either vasoconstriction or vasodilation. Vasopressors, like endothelin-1 receptor A agonists and hypoventilation, may be beneficial, depending on the patient's specific disease. Vasodilators such as nitric oxide, phosphodiesterase type V inhibitors, endothelin-1 receptor B agonists, prostanoids, rho-kinase inhibitors, and serotonin antagonists may also be used in inhalation therapy as well (20).

The use of a helium–oxygen mixture called Heliox can be used as a treatment for pediatric patients with upper and lower airway obstructions. The reduced density of the helium and oxygen mixture provides laminar flow within the airway and reduces the work of breathing. It has been used as an adjunctive treatment in children with bronchiolitis, asthma, and croup. One study found that using Heliox: 80% helium and 20% oxygen improved delivered dose at high flows when compared to oxygen alone. This study used a non-anatomically correct model with pediatric patterns of 100 ml tidal volume, 20 breaths/min frequency, and a ventilation with an I:E ratio of 1:2 (12). That being said, recent reviews show that the use of Heliox correlates with no significant reduction in rate of intubation, no reduced rate of discharge, and no decrease in length of treatment except with infants who initially started with nasal continuous positive airway pressure (NCPAP) due to severe respiratory distress. The same report suggests that the addition of Heliox therapy is recommended only in infants with severe RSV bronchiolitis, during the first hour of treatment (21).

12.6 Pharmalogical Considerations

Preparation of the drug, such as drug particle size and the speed of delivery, can affect deposition and thus drug delivery. Altering these properties of the drug can affect the delivery system by changing inertial impaction, gravitational sedimentation, and diffusion. The smaller the particle, the farther it can travel down the respiratory tract and the more likely it is to participate in diffusion in the lower airway. Larger particles (>3 μm) are more likely to deposit via inertial impaction in the conducting zone, such as the oropharynx. The mass median diameter quantifies particle size in polydisperse aerosols, or medications with a mix of particle sizes (9).

Larger doses and smaller particles are typically delivered with more efficiency. That being said, because each inhalation device operates differently, there will be a variation in optimum particle size, respirable dose, and deposition. One drug may have several different formulations and can be delivered with different devices. Manufacturers of these drugs do not always provide recommendations on the specific formulation and device to use.

Examples of some medications available for inhalation therapy are listed in Tables 12.2–12.5.

Some common drug formulations include lactose carrier systems, liposomes, porous particles, and biodegradable polymers. These formulations are molecules designed to facilitate better delivery and absorption of the drug into target tissue. Lactose carrier systems involve mixing the drug with a sugar carrier molecule in order to improve the flow of drug from the administration device. Flow of drugs may be hindered when the surface electric forces of the powder exceed the gravitational forces that aid in deposition and absorption. The carrier molecule contains an active site that binds the drug particles but is also able to separate when the drug is administered, to allow the drug to be released into target tissue. Potential side effects may result if the lactose does not separate from the drug upon aerosol generation. This may result in unintentional deposition into the oropharyngeal region, which can cause adverse reactions when using corticosteroids. Dry powder inhalers often contain either the drug alone or in a mixture with a bulky carrier molecule, such as α-lactose monohydrate. Lactose, glucose, and mannitol are sugars approved for use as drug carriers by the FDA. For use in drug formulations, these carrier molecules can be generated as either fine or coarse particles, or a mix of both. While drug particles will bind to both fine and coarse particles, there are some differences in the outcome when using them. Therapeutic

TABLE 12.2

COPD Drugs That Can Be Delivered by MDI (22,23)

Steroids	Bronchodilators	Combination Steroid/Dilator
Beclomethasone	Albuterol	Budesonide-formoterol
Ciclesonide	Levalbuterol	Fluticasone-salmeterol
Fluticasone	Ipratropium	Mometasone-formoterol

TABLE 12.3

COPD Drugs That Can Be Delivered by DPI (22)

Steroids	Bronchodilators	Combination Steroid/Dilator
Budesonide	Albuterol	Fluticasone-vilanterol
Fluticasone	Salmeterol	Fluticasone-salmeterol
Mometasone	Tiotropium	

TABLE 12.4

Corticosteroids by DPI, MDI, or SVN (9)

Drug	Device
Beclomethasone	pMDI (≥5 YO)
Budesonide	SVN or DPI (≥6 YO)
Ciclesonide	pMDI (≥12 YO)
Flunisolide	pMDI
Fluticasone propionate	DPI or pMDI
Fluticasone furoate	DPI
Mometasone furoate	pMDI or DPI

TABLE 12.5

Other Common Drugs, Devices, and Uses (9)

Drug	Device	Potential Use
Zanamivir	DPI	Influenza A and B (≥5 YO)
Ribavirin	SPAG	Respiratory syncytial virus
Tobramycin	SVN or DPI	*P. aeruginosa* in cystic fibrosis (≥6 YO)
Aztreonam	SVN	*P. aeruginosa* in cystic fibrosis (≥7 YO)
Cromolyn sodium	SVN	Bronchial asthma prophylaxis (≥2 YO)
Mannitol	DP	Diagnostic bronchoconstrictor
Dornase Alpha, N-Acetylcysteine	SVN	Mucoactivity in cystic fibrosis
Hyperosmolar saline	SVN	Mucoactive

*SPAG is an abbreviation for *small-particle aerosol generator* and is a specialized large-volume nebulizer for the delivery of ribavirin, YO = years old

aerosol mixtures with higher ratios of fine lactose particles have been found to improve disaggregation. This is because fine particles have less surface roughness, allowing the drug to separate more readily. This leads to higher respirable fractions, meaning more efficient drug delivery. Flowability of the drug is higher when using coarse lactose particles. The addition of ternary agents to lactose formulations, such as l-leucine, is hypothesized to increase dispersibility of aerosolized drugs. L-leucine may be able to occupy some of the drugs' high-energy binding sites on lactose, leaving only low-energy binding sites for the drug itself. This leads to an overall decreased strength of interaction between the drug and lactose, and thus higher respirable fractions (24).

Liposomes can be used to enhance the sustained release of drugs in the airways or alveoli, rather than allowing rapid systemic absorption. The use of liposomes as pulmonary drug vehicles can minimize the risks associated with drugs that cause side-effects when absorbed systemically. Airway-targeted deposition using drug vehicles like liposomes can increase the absorbed dose of drug therapies. This means it may be appropriate to decrease dosing frequency, which can lead to higher levels of drug-use compliance by the patient. Historically, liposomes have been used to improve phospholipid delivery to alveolar tissue of neonates undergoing respiratory distress syndrome. Lately, liposomes are being studied for their usefulness in prolonging the release of drugs used for gene therapy and to treat lung disease. Once liposomes reach the alveoli they are cleared by macrophages. This process is different for liposome-bound drugs than for other inhaled drugs. Liposomal processing occurs in a similar manner as endogenous surfactant. When designing liposome formulations, it is important to consider polymer surface coatings that protect the liposomes from the patient's immune system in order to prolong circulation (24).

Drugs that are lipophilic will intercalate within the lipid bilayers, while lipophobic ones will only contact the interface. Drugs with intermediate solubility are not transported well by liposomes, so are not typically used in these formulations. Drugs that are weak acids or bases can be manipulated to gather in the interior of the liposome, facilitating higher levels of drug retention. The usefulness of liposome formulations in delivering antibiotics to infected lungs is being investigated. Animal studies have shown sustained release and higher susceptibility of bacteria when liposome–drug formulations were used. Liposomal formulations of tobramycin were detected in the lungs of *Pseudomonas aeruginosa* infected mice 16 hours after administration. Free tobramycin only was detectable for 15 minutes. In a similarly designed study, tobramycin was shown to reduce the colony forming units (CFU) in infected rats treated with liposomal tobramycin. The number of bacteria went from 1.4×10^6 to 4.3×10^5 CFU/lung (24). When comparing this to the increase in CFU that was found in rats treated with free tobramycin, it seems clear liposomal formulations have the potential to enhance pulmonary drug delivery and efficacy.

Other animal studies, investigating the effects of liposomal formulations of anti-asthma drugs, also found more sustained-release and fewer systemic effects when using liposomes during delivery. In human trials, liposomes were shown to improve penetration and slow clearance of the anti-asthma drug beclomethasone dipropionate. Because they are lipophilic, one would assume corticosteroids are easily made into

liposomal formulations. In actuality, using liposomes with some of these drugs, such as triamcinolone acetonide, has shown to result in no sustained release or improvement in target tissue absorption. Versions of the same drug, such as with hydrophilic pro-drug triamcinolone acetonide phosphate, do show sustained release and longer occupancy in the receptor. Considering the therapeutic value of enhancing drug delivery and sustained release, more research is needed to establish guidelines about which drugs should and should not be incorporated into liposomal formulations (24).

Liposomes can be made from endogenous pulmonary phospholipids submerged in aqueous solution. The aqueous solution becomes entrapped by either one or multiple lipid bilayers, known as unilamellar or multilamellar vesicles, respectively. Unilamellar vesicles can either be large or small. There is another type of liposome which are known as long circulating liposomes, and they typically utilize a hydrophilic polymer. Vesicular properties such as size, fluidity, charge, and method of preparation can influence the chemical behavior of a drug. Liposome size influences circulating half-life and degree of drug encapsulation. Smaller vesicles have a longer half-life and slower release rate because they are opsonized at a lower rate, compared to large vesicles. When designing liposomes for clinical use, a suggested size of 50–200 nm in diameter is recommended in order to avoid phagocytosis. The fluidity of a liposome depends on the specific phase transition temperature (T_C), which depends on the type of fatty acids chains that make up the lipid bilayer. When a bilayer is in an environment below the T_C the lipids are considered to be in the gel phase. Gel phase lipids are organized and rigid. Above the T_C, the lipids are known to be in the fluid phase or with liquid-crystalline state lipids. With this in mind, it logically follows that lipids with a high T_C (above 37 °C) make the liposome more gel-like, less fluid and therefore less leaky. Cholesterol adds to the stability of lipid bilayers and, when used at high concentrations, can make liposomes less leaky as well (24).

Porous particles are a relatively new type of formulation which use Pulmospheres™ to prolong drug circulation. Pulmospheres readily disperse and are made of phosphatidylcholine. Production of these particles is by solvent evaporation and spray-drying technique, using either polymeric or nonpolymeric excipients. Pulmospheres are large and have a low density, allowing for less aggregation and higher respirable fractions. The particles' large size protects the drug from macrophage engulfment, allowing longer time spent in the alveolar region. Using a rat model and cromolyn, only between 8% and 12.5% of macrophages contained Pulmospheres, whereas between 30% and 39% of macrophages had consumed the nonporous form of the drug. Pulmospheres have also been shown to decrease side effects by reducing oropharyngeal deposition. Cromolyn Pulmospheres formulations resulted in a respirable fraction of 68%, compared with 24% when using micronized cromolyn particles. With more research, porous particles may be used to minimize drug dose and maximize therapeutic effect. Porous particles have also been suggested to increase systemic circulation of insulin and testosterone (24).

Biodegradable polymer microspheres are also being investigated as potential drug formulations to promote prolonged sustained release. Polylactic acid (PLA) is used clinically, however, it may not be appropriate for pulmonary inhalation therapy because of its long half-life. Oligolactic acid is an oligomer of lactic acid and may be a better choice because of its shorter half-life. Hydroxypropyl cellulose (HPC) is a mucoadhesive polymer and may be used to reduce mucociliary clearance of beclomethasone dipropionate (BDP). One experiment, using powder aerosol administration on guinea pigs, showed that 180 minutes after drug administration 86% of crystalline BDP with HPC microspheres remained, whereas less than 20% remained of crystalline BDP alone. In this same experiment, eosinophil inhibition was used to measure BDP's activity. The outcomes show BDP/HPC microspheres were active for 24 hours, compared to 1–6 hours with BDP alone. Nanocarriers, like polymer microspheres, show great promise in increasing the sustained release and efficacy of corticosteroids, though research must be done on the potential toxicities of such drug carriers (24).

As you can see, there are many choices when it comes to drug class, formulation, dosing, and administration device. The right combination of choices can lead to a treatment plan that optimizes drug bioavailability and minimizes premature clearance. Differences can exist between drug output, efficiency, and particle size for different nebulizers. One study found a 10-fold difference between delivery systems' efficiency. Another study found nebulizer efficiency ranged anywhere from 30% to <5% of initial dose depending on the nebulizer used. Using a device without understanding its level of efficiency can lead to underdosing. As the quality of device technology, drug design, and delivery formulation improves, so does the quality of therapy. Selecting the proper drug and optimal device is critical in ensuring the appropriate therapeutic dose is delivered to lung tissue (24).

12.7 Pediatric Considerations

Pediatric patients require special consideration due to the wide range of age, size, breathing patterns, and cooperation level (1). Diaphragmatic breathing requires breathing muscles that do not develop until later in infancy. Sometimes it is difficult to administer aerosolized medication using the necessary devices to pediatric patients. For instance, to use a pMDI, the patient must remove the inhaler's cap, shake it with the mouthpiece facing down, breathe out, press the inhaler, and at the same time take a deep breath through the mouth for a few seconds, hold breath for several seconds to absorb the medicine into airways, relax, and repeat for as many puffs as indicated. If the patient inhales the medication too quickly it will hit the back of his/her throat and will not reach the lungs. Synchronizing a child's inhalations to the device can pose a challenge. There is still a need for more research comparing the different types of nebulizers and determining which delivers the drug most efficiently to pediatric patients, depending on the specific disease at hand.

Inhaled medications are at the forefront of pediatric pulmonary disease treatment. As mentioned prior, delivering aerosolized medicine to children is compounded by the rapid anatomical and physiological changes associated with normal growth. Children younger than 18 months are obligate nasal breathers, decreasing the effectiveness of inhaled drugs. One study used computational

fluid dynamic methods to compare the parameters between difference age groups and found significant differences in regional deposition when comparing 10-day, 7-month, 3-year, 5-year, and 63-year-old parameters. Knowing the patient's demographics, and choosing the right device and technique can optimize inhaled drug deposition. Patients with asthma, under respiratory distress requiring invasive mechanical or non-invasive ventilation support, and those requiring transnasal support are only a few subsets that can benefit from improved delivery of inhalation drugs (12). Most pediatric studies are done in vitro with a simulated apparatus because radiolabeled deposition and pharmacokinetic studies can be challenging in children (12). Many studies are still done only in adults and should be repeated with parameters set for children. In addition, the studies that are being done lack a consistency between parameters dictated for the same age group.

Some inhaled drugs are used in ways not directly stated as proper usage in order to make them more therapeutically beneficial for different age groups or support devices (12). More research should be done on pharmaceutical guidelines and the optimization of aerosol drug particle size in order to enhance drug deposition in pediatric patients. When reviewing data on drug deposition it is important to account for differences between loading doses or look at absolute doses and percentages for accurate comparison. A final consideration that should be made with pediatric patients is the crucial role education plays for both patients and practitioners. Patients need to know how to deliver the medication themselves or have a legal guardian that will understand and be able to administer the medication when needed. Health care providers need to be aware of what devices exist, and how to use the chosen device properly, so they can educate patients as a part of the treatment plan. Providers should also know the options available and limitations that may exist for their patients that make one device a better choice over another. Some of these limitations include drug and device availability, cost, ease of use, patient cooperation, and acceptability by family (12).

12.8 Conclusion

This chapter aimed to clarify differences between aerosol devices and drug administration techniques for pediatric patients. Several studies using spontaneously breathing tracheostomy models were discussed in order to understand the best way to treat both pulmonary and systemic illnesses using inhalation drug therapy. The proper drug, device, and delivery method depends on the unique way in which the patient's disease presents. This chapter outlines some of options that are available, as supported in current research.

When treating pediatric patients using aerosol drug delivery, the anatomical and physiological differences between children and adults should be noted. Some of the research discussed in this chapter suggests that because children have less developed respiratory systems and muscles, different breathing patterns and mechanisms, as well as unique pharmacological considerations, there are special considerations that should be taken into account when it comes to aerosol drug delivery.

There are many different aerosolized drug delivery devices available, as well as variations in the technique of delivery, which was discussed to help familiarize readers with some of the many choices at hand. Some of the devices covered include pressurized metered-dose inhalers, soft mist inhalers, dry-powder inhalers, jet nebulizers, ultrasonic nebulizers, vibrating mesh nebulizers, breath-enhanced nebulizers, and breath-actuated nebulizers.

At some ages, children may not be able to operate these devices optimally. Some of the research discussed showed that these patients may benefit from the use of assistance in the form of T-pieces paired with resuscitation bags. AeroChambers, holding chambers, volume masks, and cascade impactors, as well as cannula design are other technical features of aerosol drug delivery that were discussed in this chapter, that can be modified to enhance the therapy of pediatric patients.

Several diseases that are sometimes treated using inhalation drug therapy were summarized because it is essential to understand what kind of therapy would best benefit the patient depending on the pathology of the disease. The most common lung disease inhalation therapy is used in children with asthma. Cystic fibrosis is also a major focus of research for inhalation drug therapies. Pneumonia, hemodynamic instability, generalized respiratory distress, and airway obstruction are some of the other conditions discussed in this chapter.

Another important factor to consider is the drug formulation being delivered. While smaller drug particle sizes are typically preferred, molecular drug carrier systems exist and are being researched in order to optimize the delivery of the drug and thus efficiency of therapy. Lactose carriers, liposomes, porous particles, and polymer microspheres were the carrier systems discussed. In general, the studies discussed indicate that carrier systems increase the bioavailability of drugs and thus greater efficiency of drug delivery to the lungs, but more research is needed on these mechanisms and what therapies drug carrier systems would be most useful for.

Overall, it is clear that more research should be done on the usefulness of inhalation drug therapy in terms of drug carrier formulation, device, and technique in order to optimize the way aerosolized drugs are being administered to pediatric patients, as well as to assess the usefulness of this specialized mode of delivery in treating systemic diseases.

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