Delivery of Inhaled Medication in Children: Revisiting Pharmacological and Practical Issues for Better Health Outcome

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Abstract

For safe and effective therapy of respiratory disorders in children, delivering the medication at the site of disease i.e. directly into the respiratory tract via aerosolized medication is critical. But, the anatomical and physiological differences in the respiratory tract of infants/children and adults make the delivery of aerosolized medication complicated. This review article give an overview of the delivery of inhaled medication in children and discuss the pharmacological and specific clinically relevant aspects of medication delivery using nebulizers, pressurized metered dose inhalers (MDIs), and dry powder inhalers (DPIs) in children. As a physician, one should always keep in mind the various factors like properties of the device, aerosol particle, patient factors such as disease state, ventilatory pattern, and administration technique that can affect drug deposition via aerosol delivery devices.

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Introduction

The health of children is very precious for their parents. In recent times, a surge in respiratory disorders has been noted in infants and children. For safe and effective therapy of respiratory disorders including asthma, it may be prudent to deliver the medication directly into respiratory tract via aerosolized medication. Drugs commonly used for respiratory disorders like bronchodilators, antibiotics, glucocorticoids and mucolytic agents can be easily administered via aerosol using a range of aerosol-generating devices (1-4). Also, the indications for aerosol therapy will broaden in future as novel macromolecular medications will be delivered via the respiratory tract for the treatment of both pulmonary and systemic disorders (5, 6). But, the anatomical and physiological differences in the respiratory tract of infants/children and adults make the delivery of aerosolized medication complicated (7-9). Hence, a thorough knowledge of the correct usage and limitations of the various aerosol delivery systems, and anatomical considerations affecting aerosol delivery in infants and children becomes critical (10, 11). To assess the information related to pharmacological and practical issues of delivery of inhaled medication in children, the articles were searched on Pubmed, Embase, Web of Science, Google Scholar, and DOAJ databases from December 20, 2023 to December 31, 2023. The keywords and their MeSH words were used in the search, which included aerosols (all fields), respiratory system abnormalities (MeSH), children (MeSH), and aerosol delivery system (all field). The search was done in the advanced mode using the Boolean operator "OR" and "AND". The free full-text of articles written in English language was used to extract the information. This review article gave an overview of the delivery of inhaled medication in children and specific clinically relevant aspects of medication delivery using nebulizers, pressurized metered dose inhalers (MDIs), and dry powder inhalers (DPIs).

Lung Diseases Managed Using Aerosol Therapy

A wide range of pediatric disorders can be treated effectively using aerosol therapy as a central component of management. Examples include: a) Obstructive airway diseases, including asthma, congenital emphysema, bronchiectasis, and bronchiolitis; b) Processes that

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result in acute upper airway obstruction, usually croup or postextubation upper-airway edema; c) Chronic lung diseases, including bronchopulmonary dysplasia and cystic fibrosis; d) Infectious diseases, including Pneumocystis jirovecii (previously carinii) pneumonia (treatment and prophylaxis), respiratory syncytial virus infection, and some pulmonary fungal infections (12-15). Less common indications for aerosol therapy include intractable cough, which may respond to inhaled lidocaine, and administration of analgesia in the setting of palliative care, using inhaled morphine (16, 17). In the future, aerosol delivery of gene constructs could be an important component of therapy for genetic diseases (5).

Properties of an Ideal Aerosol Therapy Device

The ideal aerosol delivery device varies depending upon the medication to be administered and the clinical situation. To maximize the advantages of inhaled medications described above, the device selected should be: a) Deliver an adequate dose of medication to the lungs; b) Minimize oropharyngeal deposition; c) Minimize systemic side effects; d) Match the needs of the patient; e) Be simple for the patient to use; f) Cost effective.

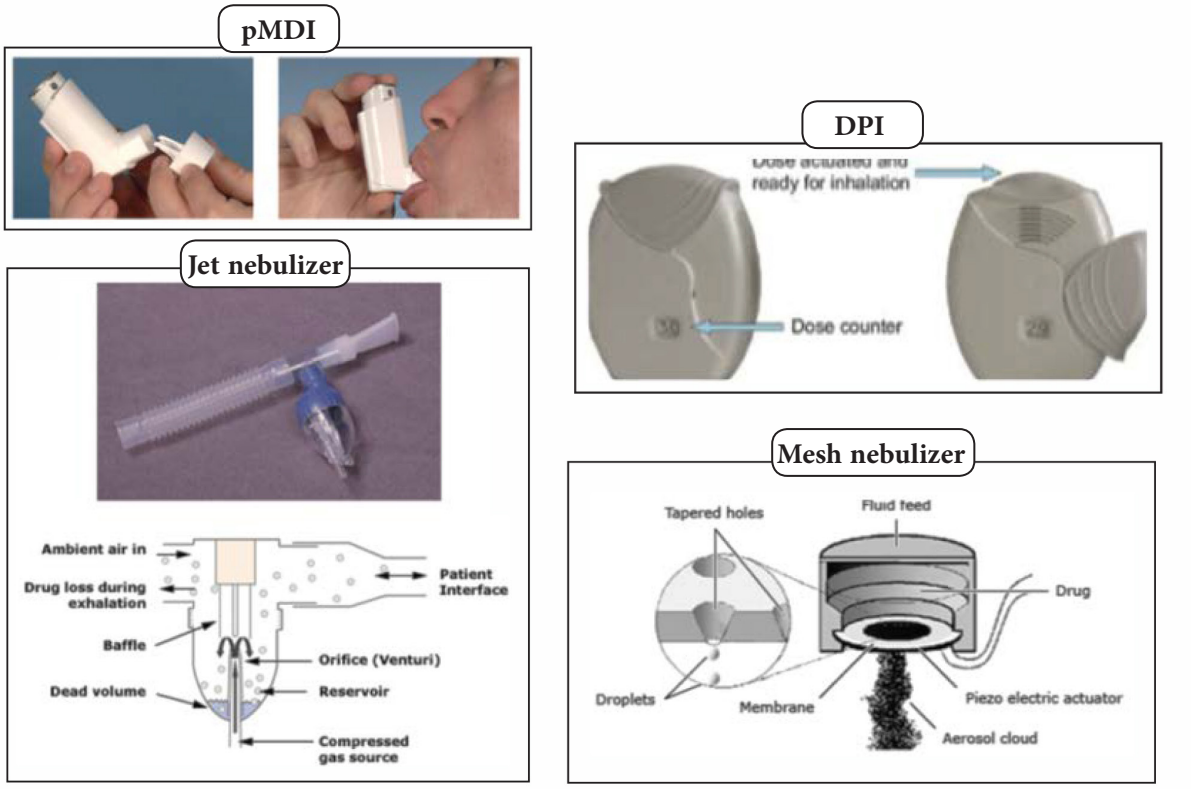
Types of Aerosol Delivery Devices

Three types of aerosol delivery devices (Figure 1) are widely employed in the management of children with respiratory disease: a) Nebulizers, which use a jet flow of driving gas, ultrasound, or vibrating membrane to aerosolize medications; b) Pressurized metered dose inhalers (MDIs); c) Dry powder inhalers (DPIs). The comparison between the various aerosol delivery devices are mentioned in Table 1. The advantages and disadvantages of commonly available aerosol devices are mentioned in Table 2.

Choosing the Best Aerosol Device by Age

The nebulizer or pMDI with valved holding chambers (VHC) is the best aerosol therapy in infants <4 years old. Although nebulizers are more tolerable than pMDI, breath-actuated nebulizers, breath-actuated pMDIs, or DPIs are not reliable in this group age. With nebulizers and pMDIs, the mask is preferable than in children younger than 3 years of age. During aerosol therapy, when nebulizers are used, a hood may provide comparable efficacy compared with face mask. High-flow nasal cannula (HFNC) is an alternative way in children who cannot tolerate a mask. The greater inhaled drug dose is delivered when infants are settled and breathing quietly. For children aged 4 years or more, the method of using pMDI or DPI is applicable. A broader range of aerosol devices can be mastered in children between 6 and 12 years of age including pMDI with or without VHC, DPI, and breath-actuated pMDIs. The choices of delivery in different age groups have been depicted in Figure 2.

Figure 1. Common modes of aerosol delivery



pMDI: pressurized metered-dose inhaler; DPI: dry powder inhaler.

Table 1. Comparison of pressurized metered dose inhalers with holding chamber (pMDI/HC), dry powder inhalers (DPIs), and nebulizers as aerosol delivery devices.

	pMDI/HC	DPIs	Nebulizer
Performance			
Majority of aerosol particles <5 micrometers in size	+	+	±
High pulmonary deposition	+	±	±
Low mouth deposition	+	±	–
Reliability of dose	+	±	±
Not compromised by humidity	+w	–	+
Physical and chemical stability	+	+	+
Breath actuated	–	+	–
Low risk of contamination	+	+	–
Convenience			
Lightweight, compact	+	+	–
Multiple doses	+	+	–
Dose counter	±	+	–
Easy and quick operation	±	±	–
Suitable for all ages	+	–	+

pMDI: pressurized metered-dose inhaler; HC: holding chamber; DPI: dry powder inhaler.

Table 2. Advantages and disadvantages of various aerosol devices.

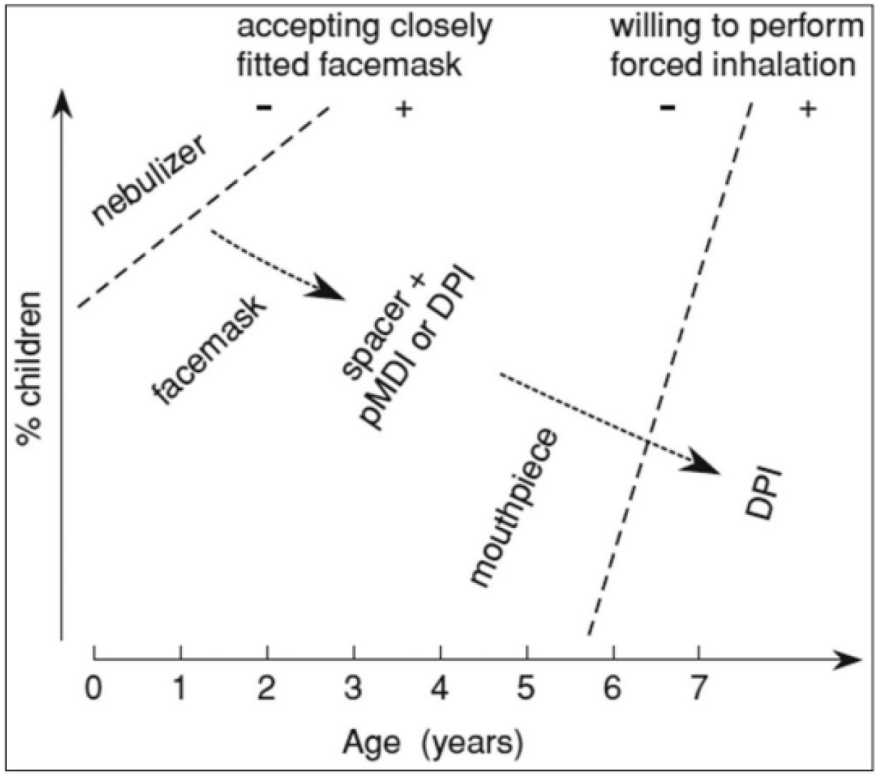
Type	Advantages	Disadvantages
Jet nebulizer	▪ Patient coordination not required ▪ High doses possible	▪ May be more expensive than pMDI ▪ More time required ▪ Contamination possible ▪ Device preparation required before treatment ▪ Not all medications available ▪ Less efficient than other devices (dead volume loss)

Table 1. Continued

Type	Advantages	Disadvantages
Mesh nebulizer (eg, Aeroneb, eFlow, Omron MicroAir, I-neb)	▪ Patient coordination not required ▪ High doses possible ▪ Quiet ▪ Faster delivery than jet nebulizer ▪ Portable, battery operated	▪ Expensive ▪ Contamination possible ▪ Device preparation required before treatment ▪ Cleaning required after dose ▪ Not all medications available
Ultrasonic nebulizer (eg, OPTI-NEB, Beetle Neb, Lumiscope, MiniBreeze)	▪ Patient coordination not required ▪ High doses possible ▪ Small dead volume ▪ Quiet ▪ No drug loss during exhalation ▪ Faster delivery than jet nebulizer	▪ Expensive ▪ Contamination possible ▪ Prone to malfunction ▪ Device preparation required before treatment ▪ Cannot use with medications in suspension (eg, budesonide)
Pressurized metered dose inhaler (pMDI)	▪ Convenient ▪ May be less expensive than nebulizer ▪ Portable ▪ More efficient than nebulizer ▪ No drug preparation required ▪ Difficult to contaminate	▪ Patient coordination essential ▪ Patient actuation required ▪ High pharyngeal deposition ▪ Difficult to deliver high doses ▪ Not all medications available
pMDI with holding chamber	▪ Less patient coordination required ▪ Less pharyngeal deposition	▪ More expensive than pMDI alone ▪ Less portable than pMDI alone
Dry powder inhaler (DPI)	▪ Less patient coordination required ▪ Convenient ▪ Propellant not required ▪ Portable ▪ Breath-actuated	▪ Requires moderate to high inspiratory flow ▪ Some units are single dose and need daily loading ▪ Can result in high pharyngeal deposition ▪ Not all medications available ▪ Cannot be used effectively in mechanically ventilated patients
Soft mist inhaler (SMI)	▪ Higher lung deposition than pMDIs or jet nebulizers ▪ Less pharyngeal deposition than pMDIs ▪ Longer duration of spray ▪ Low risk of contamination ▪ Propellant not required	▪ Requires actuation by patient ▪ Needs coordination between breathing and actuation* ▪ Requires loading of cartridge into inhaler before first use ▪ Not all medications available ▪ Cannot be used effectively in mechanically ventilated patients

*The relatively slower moving and longer duration spray from a SMI makes it easier for a patient to coordinate breathing and actuation compared to a pMDI.

Figure 2. Choices of different aerosol delivery as per age groups.



Factors affecting drug deposition via Aerosolized Drug Delivery

A number of factors influence the ultimate amount of medication delivered to the appropriate anatomic region within the lung. Some of the important factors are: a) **Properties of the device:** Devices vary greatly in their efficiencies in delivering particles to the lungs. From 6 to 60 percent of the total dose of medication is delivered to the peripheral airways when these devices are used optimally (18). b) **Aerosol properties:** Aerosol particles are characterized by their mass median aerodynamic diameter (MMAD) (19, 20). The particles with MMAD less than 0.8 micrometers generally are exhaled. Particles with MMAD of 0.8 to 2 micrometers are optimal for alveolar deposition, which occurs largely as a result of gravitational sedimentation (7, 21). Particles with a MMAD between 2 and 5 micrometers are optimal for deposition in the lower airway and are deposited largely by inertial impaction with airway structures. Particles with a MMAD greater than 5 micrometers are deposited largely in the oropharynx. c) **Properties of medication to be delivered:** The ultimate effect of the dose is dependent upon the site of deposition of the drug within the lung, the rate of drug clearance from the airway, and the site of action of the medication (18). To be effective, drugs must be able to withstand the shear forces required to generate the aerosol and often must penetrate the mucus layer and airway mucosa to reach their target receptors or cells (5). d) **Disease state and ventilatory pattern:** Anatomic and pathologic factors, as well as ventilatory patterns, alter the efficiency of aerosolized drug delivery. Aerosol particles may be deposited in the central, rather than lower, airways in diseases that are associated with decreased airway caliber such as asthma. In a study of infants with acute bronchiolitis, only 1.5 percent of aerosolized drug released from the nebulizer was deposited in the lung and 0.6 percent penetrated to the peripheral airways (22). Partly for this reason, bronchodilators are not routinely recommended for treatment of bronchiolitis. However, most of this information is based upon studies of inhalers containing chlorofluorocarbon (CFC) propellants. Penetration into peripheral airways appears to be better with the hydrofluoroalkane propellants (HFAs) that have replaced CFCs, even in patients with significant obstructive airway disease (23). Diseases causing mucus plugging or atelectasis, such as cystic fibrosis, may lead to reduction and marked heterogeneity in the distribution of particle deposition. Other factors such as tidal volume, breath-holding time, respiratory rate, and nose versus mouth breathing can dramatically alter the deposition of aerosolized particles in the lungs (7, 24). e) **Patient**

technique, acceptance, and preference: Improper technique is a common cause for a suboptimal response to aerosolized medication, and poor understanding or acceptance may lead to noncompliance. Rapid inspiration from metered dose inhalers (MDIs) may increase inertial impaction of droplets in the central airways and decrease lung delivery (24). Patient education is essential for the effective use of any aerosol delivery device (1). Furthermore, patient factors such as weakness, severe arthritis or contractures, and altered mental status may mandate the use of specific delivery devices.

Advantages of Aerosolized Drug Delivery

There are several advantages to delivering drugs by aerosol rather than systemically: a) Delivery of agents directly to their sites of action decreasing the dose required for therapeutic effect; b) Faster onset of action (compared with intravenous delivery) of bronchodilator agents, allowing more rapid reversal of acute bronchoconstriction; c) Reduced systemic bioavailability minimizing side effects.

Special Considerations in Infants and Young

The deposition of medication in peripheral airways and alveoli is reduced in infants and young children, presumably due to their smaller airways, faster respiratory rates, and lower tidal volumes, which combine to lower the resident time of small particles in the airway (7-9, 25, 26). Following are few special clinically relevant factors related to aerosol therapy in infants and young children: a) **Dose:** Data suggest that drug deposition in children older than five to six years of age is similar to that observed in adults, and identical doses in children and adults result in similar plasma concentrations (18, 27). Thus, aerosol doses generally do not need to be decreased, except possibly in very young children. However, it is probable that variability exists based upon the specific medication used, drug delivery technique (tidal volume breathing compared with inspiratory breath hold), and delivery device employed. The output of the aerosol-generating device may exceed inspiratory flow rate in children younger than six months of age, resulting in the loss of air entrainment (mixing of inspired air with nebulizer output) and a higher concentration of drug delivered (26). Overall, this effect can lead to a higher inhaled dose per kilogram of body weight in the infant younger than six months of age, increasing the possibility of side effects, although increased side effects have not been reported in this age group, nor are there recommendations to decrease any drug dose because of this effect.

b) **Respiratory pattern:** Normal tidal breathing results in the most efficient delivery to the airways. Crying markedly reduces aerosol delivery to the lungs; therefore, in general, aerosols should not be administered to crying children (28, 29). An alternative in these infants and children is to administer aerosols while they are sleeping (30). However, lung deposition of aerosolized drugs may be reduced in a nose-breathing sleeping infant (31). Furthermore, a "real-life" feasibility study of aerosol delivery via metered dose inhaler (MDI) and masked holding chamber to sleeping infants and young children found that aerosol delivery during sleep offered no advantage for most children due to frequent awakenings associated with poor cooperation and difficulty with the proper placement of the mask due to sleep position (32). Thus, aerosol administration during sleep may be tried for uncooperative infants and children, but parents should be informed that the success rate may be low. Breath-actuated devices and dry powder inhalers (DPIs) should be avoided in infants and toddlers due to their inability to generate an adequate inspiratory flow rate to reliably aerosolize the medication (18).

c) **Interface:** The interface between the aerosol-generating device and the patient is an important, and often overlooked, component of effective therapy. Administration of aerosols by a mouthpiece rather than a facemask is generally preferred due to improved drug delivery to the lungs by as much as two-fold (33). However, most children will not be able to reliably breathe through a mouthpiece until approximately four years of age, and patient technique with a mouthpiece must be assessed prior to switching from a facemask (34). In addition, delivery by facemasks or mouthpieces has been shown to provide similar clinical responses when administering bronchodilators in children with acute asthma (35) or nebulized budesonide in chronic asthma (36). Finally, delivery of fluticasone propionate via an MDI with an antistatic valved holding chamber is similar when using either a mouthpiece or facemask in children up to nine years of age, and both are associated with higher delivery compared with direct actuation into the mouth (37). These devices may be associated with higher systemic concentrations of glucocorticoids and an increased risk of side effects, particularly with higher drug doses. Thus, doses should be adjusted to the lowest that maintains asthma control. Poor patient cooperation leads many parents to use blow-by techniques for aerosol delivery. However, removing the facemask just 1 cm from the face may reduce the inspired dose by approximately

50 percent, and a 2 cm distance results in an 80 percent reduction (24). When a facemask is used either with a spacer or nebulizer, it should be placed snugly and tightly fitted over the face, as even a small leak may reduce the inhaled mass of drug to <0.5 percent of the total dose (38). The nose is an efficient filter for particles in aerosol. Thus, when using a facemask, any nose breathing is associated with increased deposition in the upper airway (24, 39). This may lead to more systemic side effects due to greater drug absorption from the upper airway. In addition, this can reduce drug efficacy because of decreased deposition in the lower respiratory tract (1, 35).

Minimally invasive surfactant therapy (MIST)

Minimally invasive surfactant therapy (MIST) is used to deliver exogenous surfactant to preterm neonates with respiratory distress syndrome (40, 41). Various studies have shown that use of MIST improved respiratory outcomes in moderate to late preterm neonates with respiratory distress syndrome (42-45).

Conclusion

Aerosol therapy devices will be the future mode of drug delivery for respiratory disorders. Presently, there are three main types of aerosol delivery devices used for optimal delivery of drugs in the management of children with respiratory disease: nebulizers pressurized metered dose inhalers (MDIs), and dry powder inhalers (DPIs). As a clinician, we should always keep in mind the various factors like properties of the device, aerosol particle, patient factors such as disease state, ventilatory pattern, and administration technique that can affect drug deposition via aerosol delivery devices. Some clinically relevant points worth noting are: a) Dose of aerosol need not be decreased except possibly in very young children. b) Crying markedly reduces aerosol delivery to the lungs, it is better to give the aerosolized drug while they are sleeping in children who tend to cry with administration. c) Administration of aerosols by a mouthpiece rather than a facemask is generally preferred in children due to improved drug delivery to the lungs. Due to the advancement in technology, even for genetic diseases, aerosol delivery of gene constructs could be a potential component of therapy in the future.

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Conflict of interest

The author declares no conflict of interest, financial or otherwise.

References

1. Fink JB. Aerosol device selection: evidence to practice. Respir Care. 2000; 45:874.
2. Dolovich MA, MacIntyre NR, Anderson PJ, et al. Consensus statement: aerosols and delivery devices. American Association for Respiratory Care. Respir Care. 2000; 45:589.
3. Hess D. Aerosol therapy. Respir Care Clin N Am 1995; 1:235.
4. Roche N, Huchon GJ. Rationale for the choice of an aerosol delivery system. J Aerosol Med. 2000; 13:393.
5. Rubin BK. Experimental macromolecular aerosol therapy. Respir Care. 2000; 45:684.
6. Newhouse MT, Corkery KJ. Aerosols for systemic delivery of macromolecules. Respir Care Clin N Am. 2001; 7:261.
7. Rubin BK, Fink JB. Aerosol therapy for children. Respir Care Clin N Am. 2001; 7:175.
8. Everard ML. Aerosol delivery in infants and young children. J Aerosol Med. 1996; 9:71.
9. Cole CH. Special problems in aerosol delivery: neonatal and pediatric considerations. Respir Care. 2000; 45:646.
10. O'Callaghan C, Barry PW. Asthma drug delivery devices for children. BMJ. 2000; 320:664.
11. Brocklebank D, Ram F, Wright J, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. Health Technol Assess. 2001; 5:1.
12. Diot P, Dequin PF, Rivoire B, et al. Aerosols and anti-infectious agents. J Aerosol Med. 2001; 14:55.
13. Gilbert BE. Liposomal aerosols in the management of pulmonary infections. J Aerosol Med. 1996; 9:111.
14. Roth C, Gebhart J, Just-Nübling G, et al. Characterization of amphotericin B aerosols for inhalation treatment of pulmonary aspergillosis. Infection. 1996; 24:354.
15. Simonds AK, Newman SP, Johnson MA, et al. Alveolar targeting of aerosol pentamidine. Toward a rational delivery system. Am Rev Respir Dis. 1990; 141:827.
16. Sherman JM. Breaking the cycle: lidocaine therapy for habit cough. J Fla Med Assoc. 1997; 84:308.
17. Cohen SP, Dawson TC. Nebulized morphine as a

treatment for dyspnea in a child with cystic fibrosis. Pediatrics. 2002; 110:e38.

18. Le Souëf P. The meaning of lung dose. Allergy. 1999; 54:93.

19. Brain JD, Valberg PA. Deposition of aerosol in the respiratory tract. Am Rev Respir Dis. 1979; 120:1325.

20. Dolovich M, Smaldone GC. Estimating the particle size characteristics of therapeutic aerosols. J Aerosol Med. 1999; 12:215.

21. Newhouse MT, Ruffin RE. Deposition and fate of aerosolized drugs. Chest. 1978; 73:936.

22. Amirav I, Balanov I, Gorenberg M, et al. Beta-agonist aerosol distribution in respiratory syncytial virus bronchiolitis in infants. J Nucl Med. 2002; 43:487.

23. Zeidler M, Corren J. Hydrofluoroalkane formulations of inhaled corticosteroids for the treatment of asthma. Treat Respir Med. 2004; 3:35.

24. O'Callaghan C. Delivery systems: the science. Pediatr Pulmonol Suppl. 1997; 15:51.

25. Barry PW, O'Callaghan C. Nebuliser therapy in childhood. Thorax. 1997; 52:S78.

26. Collis GG, Cole CH, Le Souëf PN. Dilution of nebulised aerosols by air entrainment in children. Lancet. 1990; 336:341.

27. Onhøj J, Thorsson L, Bisgaard H. Lung deposition of inhaled drugs increases with age. Am J Respir Crit Care Med. 2000; 162:1819.

28. Iles R, Lister P, Edmunds AT. Crying significantly reduces absorption of aerosolised drug in infants. Arch Dis Child. 1999; 81:163.

29. Wildhaber JH, Dore ND, Wilson JM, et al. Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children. J Pediatr. 1999; 135:28.

30. Janssens HM, van der Wiel EC, Verbraak AF, et al. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? J Aerosol Med. 2003; 16:395.

31. Clarke JR, Aston H, Silverman M. Delivery of salbutamol by metered dose inhaler and valved spacer to wheezy infants: effect on bronchial responsiveness. Arch Dis Child. 1993; 69:125.

32. Esposito-Festen J, Ijsselstijn H, Hop W, et al. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? Chest. 2006; 130:487.

33. Nikander K. Drug delivery systems. J Aerosol Med. 1994; 7:S19.

34. Amirav I, Newhouse MT. Review of optimal characteristics of face-masks for valved-holding chambers (VHCs). Pediatr Pulmonol. 2008; 43:268.

35. Lowenthal D, Kattan M. Facemasks versus mouthpieces for aerosol treatment of asthmatic children. Pediatr Pulmonol. 1992; 14:192.

36. Mellon M, Leflein J, Walton-Bowen K, et al. Comparable efficacy of administration with face mask or mouthpiece of nebulized budesonide inhalation suspension for infants and young children with persistent asthma. Am J Respir Crit Care Med. 2000; 162:593.

37. El Mallah MK, Hendeles L. Delivery of medications by metered dose inhaler through a chamber/mask to young children with asthma. Pediatr Allergy Immunol Pulmonol. 2012; 25:236.

38. Erzinger S, Schueepp KG, Brooks-Wildhaber J, et al. Facemasks and aerosol delivery in vivo. J Aerosol Med. 2007; 20:S78.

39. O'Callaghan C, Barry PW. The science of nebulised drug delivery. Thorax. 1997; 52:S31.

40. More K, Sakhuja P, Shah PS. Minimally invasive surfactant administration in preterm infants. A meta-narrative review. JAMA Pediatr. 2014; 168: 901–8.

41. Strong P, Ito K, Murray J, Rapeport G. Current approaches to the discovery of novel inhaled medicines. Drug Discov Today. 2018;23:1705 17.

42. Roberts CT, Halibullah I, Bhatia R, et al. Outcomes after introduction of minimally invasive surfactant therapy in two Australian tertiary units. J Pediatr. 2020; 229: 141–6.

43. Dargaville PA, Ali SKM, Jackson HM, Williams C, De Paoli AG. Impact of minimally invasive surfactant therapy in preterm infants at 29-32 weeks' gestation. Neonatology. 2018; 113: 7–14.

44. Owen LS, Manley BJ, Davis PG, Doyle LW. The evolution of modern respiratory care for preterm infants. Lancet. 2017; 389: 1649–59.

45. Al Moamary MS, Alhaider SA, Alangari AA, et al. The Saudi Initiative for Asthma – 2019 Update: Guidelines for the diagnosis and management of asthma in adults and children. Ann Thorac Med. 2019;14:3-48.

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