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REVIEW
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Inhaled Pharmacotherapy for Neonates: A Narrative Review

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What is known about this topic?

The inhaled route for drug administration in neonates offers several advantages over the systemic routes. Inhaled medications are varied and often used off label. Also, the literature is scattered and the levels of evidence little known.

What this study adds on this topic?

Bronchodilators, epinephrine, corticosteroids, anti-inflammatory agents, pulmonary vasodilators, mucolytics, colistin and, more recently, surfactants, are the most commonly used inhalation agents in neonates. Because of the limited data from studies and the absence of rigorous tests, all these drugs are often used off-label in neonates. They have the advantage of fewer systemic effects, but they have a low evidence of efficacy.

ABSTRACT

The inhaled route for drug administration in neonates offers several advantages over the systemic routes, since it delivers medications directly to the diseased organ, enabling higher doses locally with less systemic toxicity. Respiratory drugs can be administered in both ventilated and non-ventilated term and preterm infants. This review was carried out using selected literature, with a focus on the most used inhaled pharmacological agents in neonatal care, summarizing, with levels of evidence (LoE), their indications, doses, administration schedules, and main adverse effects. Information is given on several inhaled drugs, namely albuterol, budesonide, ipratropium bromide, sodium cromoglycate, racemic epinephrine, nitric oxide, treprostinil, iloprost, epoprostenol, colistin, rhDNase, hypertonic saline, and calfactant. A summary of the main and most recent published studies on each of these inhaled pharmacological agents is also presented.

Keywords: Albuterol, budesonide, calfactant, colistin, epoprostenol, hypertonic saline

INTRODUCTION

Respiratory problems are the most common reasons for admission to a neonatal intensive care unit (NICU).[1] The neonate has unique respiratory physiological characteristics such as small airway caliber, few collateral airways, compliant chest wall, poor airway stability, and low functional residual capacity. The pathologies affecting the newborn's lung are also different from the many others observed later in life. Respiratory care has to be individualized and needs to be adapted to the patient's characteristics, namely gestational age, the clinical condition, associated comorbidities, and the overall prognosis.[2,3]

There is an increasing trend in the NICUs to use non-invasive ventilation modes; however, invasive ventilation is still often necessary for treating preterm and term infants with respiratory insufficiency.[4,5] The pharmacological agents administered by the respiratory route, in aerosol (a suspension of fine solid or liquid particles in gas dispensed from a pressurized container) or by nebulization (reduction of a medicinal solution to a fine spray) are often used during and after mechanical ventilation in order to improve pulmonary mechanics and facilitate ventilation. The administration of drugs directly into the respiratory tree has been used since the early 1950s, to reach the target organ or when other routes are unavailable.[6] For most pharmacological agent profiles, the results from animal and adult studies are extrapolated to neonates. In literature, the data from different studies and interventions of respiratory drug delivery in ventilated infants demonstrate a reduced need for systemic glucocorticoids,[7] improved oxygenation,[8] and increased fluid resorption.[9] Moreover, the results from some studies of inhaled pharmaceutical aerosols in infants, conducted for different purposes, have demonstrated no measurable benefits.[10,11]

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Table 1. Levels of evidence (www.escardio.org).

Level of Evidence (LoE)	Description
A	Information collected from several randomized clinical trials or meta-analysis
B	Information collected from a single randomized clinical trial or extended non-randomized studies
C	Consensus opinion of specialists and/or small studies, retrospective studies, and records

Pharmacokinetics and pharmacodynamics exhibit considerable interindividual variability among neonates.[12] Because of the limited data and the absence of rigorous tests in neonates, these drugs are often used off-label. The inhaled route offers several significant advantages over the systemic routes of drug administration, since it delivers medication directly to the diseased organ, enabling higher doses locally with less systemic toxicity, and more rapid onset of action. However, there is low evidence about the efficacy. The disadvantages include possible irritant effects on airways, limitation of medication dose due to airway symptoms, and delivery systems that can be cumbersome and time consuming, and possibly very costly.[13]

This review was carried out in order to summarize the characteristics and usual indications of the main pharmacological therapies used by the respiratory route in neonates admitted to NICUs. The levels of evidence (LoE) suggested by the European Society of Cardiology (www.escardio.org) were used (Table 1).

BRONCHODILATORS

Historically, beta-2 agonists were considered of little efficacy in children below 2 years of age, because of the lack of beta-2 receptors on the bronchial mucosa. Beta-2 agonists were studied in the early 1980s for the prevention or early treatment of bronchopulmonary dysplasia (BPD) in preterm infants, and although a *Cochrane* review (2001)[14] demonstrated no significant effect on the outcome, several beta-2 agonists are still widely used in NICUs with different administration schedules.[6]

Today, it is known that muscle tissue is present in airways as early as 23 weeks gestation, at all levels of the conducting airways. The infants at 25-week gestation have a quantity of airway muscle relative to airway circumference, similar to that of term infants. The severity of BPD is nowadays defined by the arrest in pulmonary growth, the so-called new BPD. Preterm infants with BPD present some degree of airway muscle hypertrophy, and bronchospasm in very low birth weight infants is possible since the first days of life.[15-22]

Preterm infants often require oxygen supplementation, and are therefore exposed to oxidative stress. Following oxygen exposure, preterm infants frequently develop chronic lung disease and have a significantly increased risk of bronchospasm.[23]

Compared to adults, preterm and term neonates possess a relatively higher number of goblet cells that express mucus, and fewer ciliated airway cells to assist in the clearance of airway secretions.[24]

ALBUTEROL (SALBUTAMOL)

Albuterol is the most commonly used bronchodilator in NICUs. It is a beta-2 adrenergic short-acting agonist that relaxes bronchial smooth muscle, with little effect on heart rate (minor beta-1 stimulation). It stimulates the production of intracellular cyclic AMP, enhancing the binding of intracellular calcium to the cell membrane and endoplasmic reticulum, resulting in bronchodilation, improved compliance, and reduced resistance of the airways. It also enhances mucociliary clearance and drives potassium intracellularly. It is used to relieve or prevent bronchospasm, and to treat hyperkalemia (LoE A). It can be administered by nebulization, by a metered dose inhaler (MDI) with a spacer device, enhancing its selectivity. The intravenous and oral routes are rarely used in neonates. The metabolism is in the liver. The main adverse effects are tachycardia, arrhythmia, tremor, hypokalemia, and irritability. Albuterol administration should not be considered when the heart rate is over 180/minute. Tolerance may develop as soon as 1 week after starting the therapy, especially when administered orally.[25-31]

Albuterol has been used to prevent and treat bronchospasm in preterm infants developing BPD. A 2016 *Cochrane* collaboration systematic review concluded that there are insufficient data for a reliable assessment of the use of albuterol for prevention of BPD (LoE A).[32] Bronchodilators including albuterol are frequently administered to infants with established or developing BPD, with increasing use during the first hospital month, and in infants with positive pressure exposure (invasive and non-invasive mechanical ventilation). There is a marked variation in frequency and treatment duration among institutions.[32-34]

Based on studies showing that beta-agonists can accelerate the rate of alveolar fluid clearance, albuterol has been used for the treatment of transient tachypnea of the newborn (TTN). A 2016 *Cochrane* collaboration systematic review including 3 trials could find a reduction in the duration of oxygen therapy, but not in the need for continuous positive airway pressure or invasive mechanical ventilation, in the groups receiving nebulized albuterol versus placebo. The quality of the evidence was very low due to the paucity of trials, small sample sizes, and poor methodological quality, and the authors concluded that the evidence was not sufficient to support albuterol in the management of TTN (LoE A).[35] A study by Keles to investigate the efficacy of an inhaled beta-adrenergic agonist in TTN showed that clinical respiratory assessment, respiratory rate, oxygen saturation values, the need for supplemental oxygen therapy, blood gas pH, PO_2, and the duration of hospitalization were significantly improved in infants treated with albuterol and humidified oxygen, compared with infants administered the humidified oxygen only (LoE B).[36] A similar study by Babaei H concluded that the administration of the salbutamol can significantly improve respiratory distress 4 hours after administration and reduce the duration of hospital stay, tachypnea, and the time of enteral feeding (LoE B).[37] Malakian et al. (2018) studied the effect of albuterol on TTN and found a significant improvement in disease symptoms and a shorter hospital stay without adverse effects (LoE B).[38]

Albuterol has been used in acute viral bronchiolitis. A 2020 meta-analysis of 13 studies, including infants from 0 to

12 months, was not able to evidence any benefit and does not support its use in acute bronchiolitis (LoE A).[39]

The use of albuterol administered before surfactant in order to improve oxygenation in preterm infants with respiratory distress syndrome (RDS) was assessed in a study by Çelik et al. In this study, no significant effect of the inhaled albuterol treatment on the surfactant therapy in preterm infants with RDS was detected (LoE B).[40]

Intratracheal albuterol in addition to surfactant was shown to have a positive effect in reducing Intubation-SURfactant-Extubation (INSURE) failure in preterm infants with RDS (LoE B).[41]

As mentioned above, albuterol is one of the therapeutic possibilities for the treatment of hyperkalemia. A glucose-insulin infusion is considered a major therapeutic approach for the treatment of hyperkalemia, but affects the stability of blood sugar level. In a recent study by Saw et al., nebulized salbutamol was shown to be as efficient as glucose-insulin perfusion in the treatment of hyperkalemia, with fewer plasma glucose level fluctuations (LoE B).[42]

The doses of albuterol commonly used are reported in Table 2. In ventilated patients, if an MDI is used, the holding chamber can be placed either in the inspiratory limb of the circuit or between the "Y" and the endotracheal tube. If a vibrating mesh nebulizer (e.g., Aerogen®) is used, it should be placed within the inspiratory limb. The vibrating mesh nebulizer results in superior lung deposition of the drug, most likely from smaller residual volume and low operational gas flows (Table 3).[43]

Table 4 summarizes the most recent literature on inhaled pharmacotherapy for neonates.

IPRATROPIUM BROMIDE

It is a quaternary ammonium derivative of atropine, a potent inhibitor of the bronchoconstrictor acetylcholine. Acetylcholine also increases the production of airway mucin. Ipratropium bromide is an anticholinergic bronchodilator used in some NICUs as an adjunctive therapy for acute bronchospasm. When administered by inhalation, it is poorly absorbed into the circulation and acts as a selective bronchodilator. The combination of ipratropium with a beta-agonist produces more bronchodilation than either drug individually, and has been used in infants with BPD.[44] However, there is no evidence of long-term benefits of the use of ipratropium bromide in BPD patients (LoE A).[44-46]

Ipratropium is not useful in the treatment of acute bronchiolitis (LoE B).[47]

The author's position regarding bronchodilators in neonates is that they are not indicated in the stable patient without episodes of wheezing. They are indicated in acute episodes of bronchospasm, if the patient shows a good response to their use. The most commonly used bronchodilator is albuterol. Albuterol can also be used as an adjunctive therapy for treating severe hyperkalemia. Ipratropium can be used in acute respiratory episodes with bronchospasm, as adjuvant therapy.

SODIUM CROMOGLYCATE

Sodium cromoglycate is an anti-inflammatory agent. It is a mast cell stabilizer that prevents mast cell activation and degranulation, and also inhibits neutrophil chemotaxis and the free radical-induced neutrophil nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.[48]

Sodium cromoglycate is not indicated for the relief of acute bronchospasm, since it is an anti-inflammatory agent used for long-term therapy, and is not as effective as beta-2 agonists. It has been used as an adjunct therapy with diuretics, bronchodilators, and corticosteroids to prevent or in establishing BPD.[49]

Inhaled cromoglycate was first studied in neonates during the 1990s, and conflicting results regarding its efficacy in reducing mortality and BPD rate in preterm neonates emerged.[6] A 2017 *Cochrane* collaboration systematic review concluded that there is currently no evidence from 2 randomized trials that sodium cromoglycate, versus placebo or no intervention, has a role in the prevention of BPD, and cannot be recommended for the prevention of BPD in preterm infants (LoE A).[50]

The author's position is that sodium cromoglycate is not useful in preventing BPD in preterm infants.

EPINEPHRINE

Racemic Epinephrine (combination of levorotatory and dextrorotatory forms of epinephrine, the latter being 1/12 to 1/18 as potent as the former) stimulates both alpha and beta-adrenergic receptors on vascular smooth muscle, producing vasoconstriction and reducing edema. This mechanism of action is useful in reducing post-extubation upper airway edema and stridor after prolonged invasive ventilation, or trauma after multiple intubations. The side effects include tachycardia, arrhythmias, hypertension, peripheral vasoconstriction, hyperglycemia, hyperkalemia, metabolic acidosis, and leukocytosis. Unfortunately, there is no evidence either supporting or refuting the use of nebulized racemic epinephrine in neonates (LoE C).[51]

L-epinephrine has been tried to relieve symptoms of TTN. There is, at present, insufficient evidence to determine the efficacy and safety of epinephrine in the management of TTN (LoE C).[52]

The author's position regarding the use of nebulized racemic epinephrine in neonates with post-extubation upper airway edema and stridor is that it can be used as a therapy in association with intravenous dexamethasone.

CORTICOSTEROIDS

Corticosteroids are powerful down-regulators of inflammation and have been widely used post-natally to prevent and treat BPD. The concern for adverse outcomes with the use of systemic postnatal corticosteroids in BPD, including gastrointestinal perforation in the short term, and cerebral palsy in the long term, likely led to the widespread use of alternative routes of administration. The potential benefits of direct administration to the lungs include the sufficiency of lower medication doses compared with systemic administration, fewer systemic

Table 2. Inhaled Medications for Neonates, Indications, Doses, and Adverse Effects

Group	Mechanism of Action and Indications	Doses	Adverse Effects
Bronchodilators **Albuterol** **Ipratropium bromide (Atrovent)**	**Albuterol** stimulates the production of intracellular cyclic AMP, enhancing the binding of intracellular calcium to the cell membrane and endoplasmic reticulum, resulting in bronchodilation. Prevention and treatment of **bronchospasm.** Bronchodilator in respiratory distress syndrome and bronchopulmonary dysplasia/chronic lung disease. Used for the treatment of **hyperkalemia**. A quaternary ammonium derivative of atropine, a potent inhibitor of the bronchoconstrictor acetylcholine. **Bronchodilator for adjunctive treatment of acute bronchospasm.**	**To treat bronchospasm** **Nebulization**: 0.1-0.5 mg/kg/dose every 2 to 6 hours as needed. OR: 1.25-2.5 mg/dose every 2-6 hours **MDI**: 0.1 mg/spray (100 mcg/spray) - 1 to 2 puffs every 2 to 6 hours as needed **To treat hyperkalemia** **Term/near-term infants** **Nebulization:** 1.25-2.5 mg/dose in 2 mL normal saline, every 2 to 6 hours as needed **Preterm infant** **Nebulization**: 0.4 mg/dose in 2 mL normal saline, every 2 hours until serum potassium decreases to less than 5 mmol/L (or a maximum of 12 doses) **Nebulization**: 75-175 mcg/dose nebulized every 8 hours. Dilute to 3 mL with normal saline or concurrent albuterol **MDI**: 2 (34 mcg) to 4 (68 mcg) puffs as needed every 6 to 8 hours.	Tachycardia, tremors, central nervous system stimulation, hypokalemia, hyperglycemia, hypertension, irritability. Consider not administering when heart rate is greater than 180/min. COMMENTS: Duration of action is approximately 2 to 5 hours. Titrate dose according to the effect on heart rate and improvement in respiratory symptoms. Albuterol should not be used as the sole agent for treating severe hyperkalemia; the onset of action in the treatment of hyperkalemia is approximately 20 to 30 minutes. Rebound airway hyper-responsiveness after discontinuation. Nervousness, dizziness, nausea, blurred vision, dry mouth, exacerbation of symptoms, airway irritation, cough, palpitations, rash, and urinary retention. Use with caution in narrow-angle glaucoma or bladder neck obstruction. COMMENTS: Compatible when admixed with albuterol if given within 1 hour. Bronchodilator effect may be potentiated when given with β2-agonist (i.e., albuterol).
Non-steroid anti-inflammatory **Sodium cromoglycate**	Anti-inflammatory agent; a mast cell stabilizer that prevents mast cell activation and degranulation, and also inhibits neutrophil chemotaxis and free radical-induced neutrophil NADPH oxidase. Chronic control of bronchospasm as an adjunctive therapy	Inhalation: 20 mg 3-4 times a day.	Angioedema, chest pain, flushing, rash, tachycardia, anxiety, irritability, abdominal pain, dysphagia, abnormal liver tests, dysuria, neutropenia, pancytopenia, polycythemia,
Vasoconstrictor, anti-edematous **Racemic epinephrine**	Stimulates both alpha- and beta-adrenergic receptors on vascular smooth muscle, producing vasoconstriction and reduction of edema. Post-extubation upper airway edema.	**Nebulization**: 0.25 to 0.5 mL of 2.25% racemic epinephrine diluted in 2 to 3 mL of NS.	Hypertension, tachycardia, nausea, pallor, tremor, cardiac arrhythmias, increased myocardial oxygen consumption, and decreased renal and splanchnic blood flow.
Corticosteroids **Budesonide**	Down-regulator of inflammation; used to reduce inflammation in advanced chronic lung disease	**Nebulization:** 0.25 mg 12/12 h, or 0.5 mg once daily **MDI**: 200 µg 12/12 h or 8/8 h.	Respiratory tract infection, hypertension, hyperglycemia, adrenal insufficiency, growth suppression, and osteopenia.

Vasodilators **Nitric oxide (iNO)** **Epoprostenol** **Iloprost** **Treprostinil**	iNO produces vasodilation limited to the pulmonary circulation, acting on muscle receptors of airway blood vessels; its effect is via the increase of the intracellular cGMP; intracellular cGMP induces vasodilation via many mechanisms. Treatment of term and near-term (≥34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of persistent PH of the newborn. Activates adenylate cyclase to convert ATP to cAMP, which activates protein kinase A and the exchange protein activated by cAMP (Epac) resulting in vessel relaxation. Used in PH refractory to iNO; and acute pulmonary hypertensive crisis. PH, adjunctive to iNO PH, is mostly prescribed for Outpatients; need for specialized nurses for teaching and technical support.	Begin at 20 ppm. Reduce dose to lowest possible level. Doses >20 ppm are usually not used due to increased risk of methemoglobinemia and elevated nitric dioxide (NO_2). Treat until the underlying oxygen desaturation has resolved and the infant is ready to be weaned from iNO. Abrupt discontinuation may lead to rebound pulmonary hypertension. **Weaning**: by 5 to 10 ppm every 4 hours until the patient is stable at 5 ppm, then decreasing by 1 ppm every 4 hours until discontinued. Further diagnostic testing should be sought for infants who are unable to be weaned off iNO after 4 days of therapy. **Nebulization**: 10–50 ng/kg/min, continuous nebulization (significant improvement of oxygenation index at 30 ng/kg/min) **Nebulization**: 0.5–2 mcg/kg/dose every 30 minutes to 2 hours (6–9 inhalations per day). 3–9 puffs (18–54 mcg/treatment), 4 times a day, via Opti-Neb ultrasonic nebulizer. Used in a spontaneously breathing patient. Although it is possible to deliver treprostinil in the mechanically ventilated patient, experience is very limited in neonates.	Do not use in neonates who are dependent on right-to-left shunting of blood. Direct pulmonary injury from excess levels of NO_2 and ambient air contamination may occur. May cause methemoglobinemia and elevated NO_2. The risk of adverse effects increases when iNO is given at doses >20 ppm. Conflicting data have been published on whether or not iNO inhibits platelet aggregation and prolongs bleeding time. Monitor methemoglobin levels, iNO, NO_2, and oxygen levels. Flushing, hypotension, tachycardia, agitation, infection, pain, pulmonary edema, thrombocytopenia Arterial hypotension from systemic spillover; recommended intermittent delivery. Limited experience in neonates. Cough, wheeze, headache, throat irritation, nausea, diarrhea, syncope in older children.
Antibiotics **Colistin**	Colistimethate sodium is a surface-active agent that is used to penetrate and disrupt the cell membrane of bacteria. It has demonstrated bactericidal activity against most strains of aerobic Gram-negative microorganisms, both in vitro and in clinical infections.	4–5 mg/kg/dose aerosolized for 15 minutes every 12 hours for a median of 9 days (4 to 14 days) as **adjunctive** to IV antibiotics; another described regimen: colistimethate sodium 1 million IU (33.4 mg colistin base) **monotherapy** twice daily for an average of 9.1 days (4 to 22 days)	Neither clinical nor laboratory adverse events were reported with aerosolized colistin in neonates. Serum creatinine and blood urea nitrogen remained within normal limits 72 hours after completion of colistin therapy
Mucolytics **rhDNase** **Hypertonic saline**	rhDNase, is an enzyme that selectively cleaves DNA. Purulent pulmonary secretions contain very high concentrations of extracellular DNA, released by degenerating leukocytes. rhDNase hydrolyzes this DNA to decrease the viscoelasticity of the secretions. Clinical improvements in the thickness of secretions and ventilation usually occur within 3 hours of administration. Useful in making secretions less viscous. Hypertonic saline is capable of disrupting ionic bonds within the mucus gel and reduces cross-linking and entanglements.	1.25 mL to 2.5 mL via nebulizer, or 0.2 mL/kg instilled directly into the endotracheal tube. Administer once or twice per day. 4 mL every 4 hours, nebulized or aerosolized	Desaturation and/or airway obstruction may occur due to rapid mobilization of secretions. Although very rare, cough and bronchospasm may occur.
Surfactant **calfactant**	Improvement in respiratory distress syndrome in preterm neonates with no need for intubation. Surfactants are essential for effective ventilation by modifying alveolar surface tension, thereby stabilizing the alveoli.	210 mg phospholipid/kg body weight, up to 3 treatments, at least 4 hours apart.	Mainly air-leaks, although not more frequently than with instilled surfactant.

Adapted from Taketomo et al.,[81] Young and Magnum,[82] Gomella,[83] and Bhatt-Mehta.[84]
iNO, inhaled nitric oxide; MDI, metered dose inhaler; PH, pulmonary hypertension.

Table 3. Different aerosol generators.[43]

Type	Characteristics
MDI	An aerosol cloud containing the predefined dose of the active drug ("puff") is released after pressing the propellant device. Can be administered in ventilated patients if connected through a spacer in the inspiratory limb or between the "Y" and the endotracheal tube. Can be administered by mask and spacer chamber in non-intubated patients. The efficacy expressed as inhaled dose percentage is **mid**.
Jet nebulizer	The liquid medication is turned into a thin vapor after a compressor provides an air jet flow that passes a capillary tube, transforming the liquid formulation into a jet stream. Suitable for most common medications. Must be placed in the inspiratory limb of the ventilator. The efficacy expressed as inhaled dose percentage is **low**.
Ultrasonic	Ultrasonic high-frequency vibrations created by a piezoelectric crystal pass through the medication reservoir and create the aerosol. It is not suitable for some common medications. Must be placed in the inspiratory limb of the ventilator. The efficacy expressed as inhaled dose percentage is **mid**.
Vibrating mesh	The vibratory membrane passes the medication through the microscopic holes of the membrane, creating the aerosol. Can be placed in the inspiratory limb or between the "Y" and the endotracheal tube. The efficacy expressed as inhaled dose percentage is **high**.

MDI, metered dose inhaler.

adverse effects, and a more rapid onset of action at the target organs. Corticosteroids can either be suspended in propellants and inhaled in metered doses, nebulized, or mixed with exogeneous surfactant and injected into the trachea. Inhaled or intratracheal corticosteroids are believed to attenuate the inflammatory process associated with the development and the subsequent course of BPD.[53]

Although concerns about the adverse long-term effects of these agents, such as neurodevelopmental impairment, led to recommendations against their systemic use, systemic steroids are not absolutely contraindicated.[54]

The first reported studies of inhaled steroids in neonates are from the 1990s.

BUDESONIDE

It is a potent glucocorticoid that has been used by inhalation to prevent BPD. The *NEuroSIS* trial of early inhaled budesonide led to conflicting results. Although budesonide reduced the rate of BPD, a follow-up study showed an increased risk of mortality compared with placebo.[55,56] Budesonide is now used in some NICUs to reduce inflammation in advanced chronic lung disease.[57]

A 2017 *Cochrane* collaboration systematic review, including studies with budesonide and other inhaled corticosteroids, found no evidence that early inhaled steroids confer important advantages over systemic steroids in the management of ventilator-dependent preterm infants (LoE A).[58]

More recently, corticosteroids have been tested in association with pulmonary surfactant. A meta-analysis of Zhong et al. concluded that the early administration of budesonide associated with pulmonary surfactant is an effective and a safe option for preterm infants with RDS in preventing BPD and reducing mortality, decreasing additional surfactant use (LoE A).

The appropriate dose of corticosteroid combined with pulmonary surfactant, an administration route via inhalation versus instillation, and the long-term safety need to be assessed in large trials.[59]

Onland et al. determined that the administration of inhaled corticosteroids (budesonide, beclomethasone, fluticasone, dexamethasone, and flunisolide) starting after the first week of life and until 36 weeks postmenstrual age, in 8 trials randomizing 232 preterm infants at high risk of developing BPD, was effective and safe in reducing the incidence of death and BPD as separate or combined outcomes. However, based on the results, inhalation corticosteroids initiated at ≥7 days of life for preterm infants at high risk of developing BPD could not be recommended (LoE A). The authors propose more and larger randomized, placebo-controlled trials to establish the efficacy and safety of inhalation corticosteroids.[60]

The author's position is that although there is no clear evidence, budesonide can be used to reduce inflammation and to prevent episodes of recurrent wheezing in developing BPD.

PULMONARY VASODILATORS

Off-label use of aerosolized prostacyclins and an aerosolized prostaglandin in neonates with arterial pulmonary hypertension (PH) has been reported; however, evidence from large randomized clinical trials is lacking. The amount of a given dose of aerosolized drug that is actually delivered to the lungs is often unknown, and the actual amount of drug deposited in the lungs can be affected by several factors, including patient size, nebulizer used, and placement of the nebulizer within the breathing circuit. Inhaled nitric oxide (iNO) is the only pulmonary vasodilator approved by the US Food and Drug Administration for the treatment of persistent PH of the newborn (PPHN).[61]

NITRIC OXIDE (NO)

NO was discovered in 1772 by Joseph Priestly, and the vascular smooth muscle relaxant properties of NO were discovered in 1979. In 1992, the importance of the NO discovery was recognized, with the Nobel Prize in Physiology and Medicine awarded to Furchgott, Ignarro, and Murad.[62]

Table 4. Summaries of the most recent literature on inhaled pharmacotherapy for neonates.

PharmacologicalAgent	Reference	Summary
Albuterol	Andrzejowski and Carroll (2016)[26]	In this paper, the authors discuss the pharmacology and pharmacodynamics, practical prescribing points, and some unresolved issues surrounding salbutamol use.
	Ng et al. (2016)[32]	A *Cochrane Database Syst Rev* to determine the effect of bronchodilators given as prophylaxis or as treatment for BPD on mortality and other complications of preterm birth in infants at risk for, or identified as having BPD, concluded that data are insufficient for a reliable assessment of the use of salbutamol for prevention of BPD.
	Slaughter et al. (2015)[33]	A retrospective study with the objective of identifying the factors associated with bronchodilator administration to 1429 infants with BPD, and evaluating inter-institutional prescribing patterns concluded that: (1) bronchodilators are frequently administered to infants with BPD with increasing use during the first hospital month; (2) increasing positive pressure exposure (invasive and non-invasive mechanical ventilation) best predicts bronchodilator use; (3) frequency and treatment duration vary markedly among institutions.
	Ballard et al. (2002)[30]	A survey that queried 18 aspects of albuterol administration to ventilated newborns in academic medical centers in the United States concluded that there is substantial variability among NICUs in albuterol administration, with the majority of institutions administering albuterol via MDI.
	Moresco et al. (2016)[35]	A *Cochrane Database Syst Rev* to assess whether salbutamol compared to placebo, no treatment, or any other drugs administered to treat TTN, is effective and safe in in infants born at 34 weeks' gestational age or more concluded that, at present, there is insufficient evidence to determine the efficacy and safety of salbutamol in the management of TTN.
	Babaei et al. (2019)[37]	This study aimed to evaluate the safety and efficacy of inhaled salbutamol for the treatment of TTN in 80 neonates randomly assigned into 2 groups of treatment and placebo. The conclusion was that the administration of salbutamol can significantly improve respiratory distress following 4h and reduce the duration of hospital stay, tachypnea, and the time to enteral feeding.
	Malakian et al. (2018)[38]	The study aimed to evaluate the effect of inhaled salbutamol on the clinical progression of TTN found a significant improvement in disease symptoms, in the treatment duration, hospitalization duration, need for continuous positive airway pressure therapy, and time of oral feeding initiation, without adverse effects in the treatment group vs. the placebo group.
	Çelik et al. (2018)[40]	This study evaluated whether previously inhaled salbutamol would increase the effects of surfactant (poractant alfa) on oxygenation in premature infants with respiratory distress syndrome (RDS). The effects of salbutamol therapy were evaluated by determining the duration of respiratory support, number of doses of surfactant, respiratory rate, heart rate, fraction of inspired oxygen, and partial pressure of arterial oxygen before and after salbutamol nebulization. No statistically significant difference was detected between the 2 groups. No significant effect of inhaled salbutamol treatment on the surfactant therapy in premature infants with RDS was detected.
	Dehdashtian et al. (2016)[41]	In this study, the authors hypothesized that the administration of salbutamol to increase lung fluid absorption would decrease the INSURE failure rate in newborns with respiratory distress syndrome (RDS) treated with intratracheal surfactant. Although no statistically significant differences were observed in the assessed outcomes, except for duration of hospitalization, the INSURE failure rate was lower in the salbutamol group. The authors concluded that salbutamol may improve the clinical course of newborns with RDS requiring surfactant.
	Saw et al. (2019)[42]	A study aimed to evaluate the effectiveness of salbutamol nebulization compared to glucose-insulin infusion for the treatment of non-oliguric hyperkalemia in premature infants concluded that salbutamol nebulization is not only as effective as glucose-insulin infusion for treating non-oliguric hyperkalemia in premature infants, but can avoid potential side effects such as vigorous blood glucose fluctuations.
Ipratropium bromide	Brundage et al. (1990)[44]	This study measured the response of respiratory system mechanics in ventilated infants to different doses of ipratropium bromide, ipratropium bromide plus salbutamol, and saline vehicle, delivered via nebulizer into the ventilator circuit. The greatest decrease in resistance was seen 1 to 2 hours after the administration of 175 micrograms ipratropium bromide+salbutamol.
	Karadag et al. (2008)[47]	A study aimed to investigate the efficacy of ipratropium bromide and salbutamol in the treatment of patients with moderate-severe bronchiolitis revealed that the clinical scores and oxygen saturation levels improved more rapidly in the bronchodilator groups than in the placebo group up to 24 hours, but these drugs did not have a sufficient effect to change the natural course of the disease.

Table 4. Summaries of the most recent literature on inhaled pharmacotherapy for neonates. (Continued)

PharmacologicalAgent	Reference	Summary
Sodium cromoglycate	Ng and Ohlsson (2017)50	A *Cochrane* systematic review to determine the effect of prophylactic administration of cromolyn sodium on the incidence of BPD mortality, or the combined outcome of mortality and BPD in preterm infants, concluded that there is currently no evidence from randomized trials that cromolyn sodium has a role in the prevention of CLD.
Epinephrine	Davies and Davis (2002)[51]	A *Cochrane* systematic review to assess whether nebulized epinephrine administered immediately after extubation in neonates weaned from IPPV decreases the need for subsequent additional respiratory support. No studies were identified. There is no evidence either supporting or refuting the use of inhaled nebulized racemic epinephrine in newborn infants. Randomized controlled trials are needed comparing inhaled nebulized racemic epinephrine with placebo in neonates post-extubation.
	Moresco et al. (2016)[52]	A *Cochrane* systematic review to assess whether epinephrine, compared to placebo, no treatment, or any other drugs (excluding salbutamol) is effective and safe in the treatment of TTN in infants born at 34 weeks' gestational age or more. One trial, which included 20 infants, met the inclusion criteria of this review. No differences between the 2 groups in the duration of supplemental oxygen therapy and need for mechanical ventilation were found. The author's conclusion is that at present, there is insufficient evidence to determine the efficacy and safety of epinephrine in the management of TTN.
Budesonide	Bassler et al. (2018)[55]	A RCT (*Neurosis trial*) found that among surviving extremely preterm infants, the rate of neurodevelopmental disability at 2 years did not differ significantly between infants who received early inhaled budesonide for the prevention of BPD and those who received placebo, but the mortality rate was higher among those who received budesonide.
	Bassler et al. (2015)[56]	A RCT (*Neurosis trial*) of early inhaled budesonide versus placebo for BPD prevention in 863 ELGA infants found that the incidence of BPD was lower among those who received early inhaled budesonide, but also an increase in mortality.
	Shah et al. (2017)[58]	A *Cochrane* systematic review to determine the effect of inhaled versus systemic corticosteroids administered to ventilator-dependent preterm neonates < 1500 g BW or <32 weeks GA after 2 weeks of life for the treatment of evolving BPD. The review found no evidence that inhaled corticosteroids confer net advantages over systemic corticosteroids in the management of ventilator-dependent preterm infants. Neither inhaled steroids nor systemic steroids can be recommended as standard treatment for ventilated preterm infants.
	Zhong et al. (2019)[59]	A meta-analysis designed to evaluate the efficacy and safety of early airway administration (within 2 days after birth) of corticosteroids and surfactant for preventing BPD in premature infants with neonatal respiratory distress syndrome concluded that early administration of corticosteroids and surfactant is an effective and safe option in preventing BPD and reducing mortality, decreasing the additional surfactant usage. Furthermore, the appropriate dose and duration, combined use of inhalation or instillation, and the long-term safety of airway administration of corticosteroids need to be assessed in large trials.
	Onland et al. (2017)[60]	A *Cochrane* systematic review to determine whether the administration of inhalation corticosteroids after the first week of life until 36 weeks postmenstrual age to preterm infants at high risk of developing BPD is effective and safe in reducing the incidence of death and BPD as separate or combined outcomes. Based on the results of the available evidence, inhalation corticosteroids initiated at ≥7 days of life for preterm infants cannot be recommended at this point in time. More and larger randomized, placebo-controlled trials are needed to establish the efficacy and safety of inhalation corticosteroids.
Nitric oxide	Sherlock et al. (2020)[64]	Inhaled iNO is a powerful therapeutic used in neonatology. Its use is evidence-based for term and near-term infants with persistent pulmonary hypertension; however, it is frequently used off-label both in term and preterm babies. This article reviews the off-label uses of iNO in infants. A rationale is discussed for a selective application of iNO based on physiologically guided principles, and new research avenues are considered.
	Barrington et al. (2027)[66]	A *Cochrane* systematic review to determine the effects of treatment with iNO on death, BPD, intraventricular hemorrhage, or other serious brain injury, and on adverse long-term neurodevelopmental outcomes in preterm newborn infants with hypoxic respiratory failure concluded that iNO does not appear to be effective as rescue therapy for the very ill preterm infant. Early routine use of iNO in preterm infants with respiratory disease does not prevent serious brain injury or improve survival without BPD. Later use of iNO to prevent BPD could be effective.

PharmacologicalAgent	Reference	Summary
Epoprostenol Iloprost Treprostinil	Kuch et al. (2017)[68]	A lack of definitive evidence of iNO combined with increasing health-care costs has led to the use of less costly inhaled prostacyclin as an alternative to iNO, presenting unique patient safety concerns. This review evaluates the current evidence and patient safety considerations regarding inhaled pulmonary vasodilators in the pediatric population.
	Hill et al. (2015)[69]	A number of inhaled agents have been developed to treat pulmonary hypertension; the most in current use are the prostacyclins, including epoprostenol, which has been cleared for intravenous applications, but is used off-label in acute care settings as a continuously nebulized medication. Aerosolized iloprost and treprostinil are both prostacyclins that have been increasingly used to treat pulmonary arterial hypertension.
Colistin	Çelik et al. (2012)[72]	A single-center experience with aerosolized colistin in 2 preterm and 1 term neonate with *Acinetobacter baumannii* and *Pseudomonas aeruginosa*-related VAP who were unresponsive to previous antimicrobial treatment. Authors found that aerosolized colistin was tolerable and safe, and it may be an adjunctive treatment option for resistant Gram-negative bacterial VAP in neonates.
	Hussain et al. (2020)[73]	A retrospective matched case-control study: 16 neonates with multidrug-resistant Gram-negative agent associated-VAP received intravenous+aerosolized colistin, and 16 control neonates received IV-colistin alone. Shorter duration of antibiotics, higher clinical cure and microbial eradication, along with lower ventilatory requirements, mortality rate, and colistin-induced nephrotoxicity and electrolyte imbalance were observed in the intravenous+aerosolized colistin group.
	Kang et al. (2014)[75]	Eight preterm infants (25-36 weeks) from January 2006 to December 2010 who received inhaled colistin as monotherapy for VAP due to *Acinetobacter baumannii* infection were retrospectively evaluated. Of the isolated microorganisms, all were sensitive to colistin. All patients received inhaled colistin at a dose of 1 000 000 IU (33.4 mg) twice daily for an average of 9.1 days (range, 4-22 days). All preterm infants were cured, with *Acinetobacter baumannii* eradicated from airway secretions. There were no clinical or laboratory adverse events related to colistin use.
rhDNase	Fedakar et al. (2012)[77]	A prospective study aimed to evaluate the safety of recombinant human deoxyribonuclease (rhDNase) in 22 patients with atelectasis, unresponsive to conventional treatment. Nebulized rhDNase was administered to all patients at a dose of 1 mg/m^2 twice daily for 3 days. In patients who did not respond to 3 days of treatment, endotracheal rhDNase was administered at a dose of 1 mg/m^2. A clinical and radiologic improvement of atelectasis was observed in 18 of 22 patients following 3 days of nebulized rhDNase treatment. Atelectasis relapsed in 4 patients. Following the administration of combined endotracheal and nebulized rhDNase treatment, an improvement of atelectasis was noted in all 4 recurrent cases. No adverse events were observed in patients because of the rhDNase treatment.
Hypertonic saline	Dilmen et al. (2011)[78]	A prospective study to compare and evaluate the efficacy of nebulized 3% hypertonic saline (HS) and recombinant human DNase (rhDNase) treatment for resolution of persistent atelectasis in newborns. Forty neonates were enrolled to receive either nebulized 3% HS solution ($n = 20$) or rhDNase ($n = 20$). The percentage of atelectasis resolution after 3 days treatment was 90% (18/20) in the 3% HS group and 70% (14/20) in the rhDNase group. The patients in the 3% HS group showed better improvement in clinical parameters as well.
	Zhang et al. (2015)[79]	A systematic review to assess the efficacy and safety of nebulized hypertonic saline (HS) in infants with acute bronchiolitis. Twenty-four trials involving 3209 patients, 1706 of whom received HS. Hospitalized patients treated with nebulized HS had a significantly shorter length of stay and a significantly lower post-treatment clinical score in the first 3 days of admission, compared with the 0.9% saline group. Nebulized HS reduced the risk of hospitalization by 20% among outpatients. No significant adverse events related to HS inhalation were reported.
Surfactant	Cummings et al. (2020)[80]	A prospective, multicenter, randomized, unblinded comparison trial of aerosolized calfactant (Infasurf) in neonates with RDS that required non-invasive respiratory support. Calfactant was aerosolized; 6 mL/kg (210 mg phospholipid/kg body weight) were delivered directly into the mouth. In total, 230 infants were randomly assigned to aerosol; 225 received 334 treatments, starting at a median of 5 hours. The rates of intubation for surfactant instillation were 26% in the aerosol group and 50% in the usual care group ($P < .0001$). Respiratory outcomes up to 28 days of age were no different.

BPD, bronchopulmonary dysplasia; ELGA, extremely low gestational age; iNO, inhaled nitric oxide; INSURE, intubate-surfactant-extubate; IPPV, intermittent positive pressure ventilation; MDI, metered dose inhaler; NICU, neonatal intensive care unit; RCT, randomized controlled trial; TTN, transient tachypnea of the newborn; VAP, ventilator-associated pneumonia.

Inhaled nitric oxide (iNO) produces vasodilation limited to the pulmonary circulation, acting on muscle receptors of the airway blood vessels. The technique of its administration is very expensive at present,[63] but allows avoiding the systemic hypotension of the systemic route. Its effect is via the increase of the intracellular cyclic-guanosine-monophosphate (cGMP). iNO is rapidly inactivated by hemoglobin, producing methemoglobin, and its half-life is less than 5 seconds. It has been used in near-term or term (>34 weeks of gestational age) babies, starting at 20 ppm (parts per million) with hypoxemic arterial PH (LoE A).[64] Over the last years, it has been more and more frequently used as an off-label rescue therapy in hypoxemic preterm infants.[65] A *Cochrane* collaboration meta-analysis published in 2017 concluded that iNO does not appear to be effective as rescue therapy for the very ill preterm infant. Early routine use of iNO in preterm infants with respiratory disease does not prevent serious brain injury or improve survival without BPD. The later use of iNO to prevent BPD could be effective (LoE A).[66]

PROSTACYCLINS (PGI2)

Studies on the role of prostaglandins in anaphylaxis and respiratory diseases started in the 1960s. In 1976, Vane and fellow researchers Salvador Moncada, Ryszard Gryglewski, and Stuart Bunting published the first paper on prostacyclin in *Nature*.[67] Its use in neonatal medicine started in the 1990s. These molecules are derived from arachidonic acid via the action of prostacyclin synthase, and are potent vasodilators. Epoprostenol, iloprost, and treprostinil have been used by inhalation in neonates with PH.[68]

EPOPROSTENOL

The intravenous formulation can be aerosolized and used off-label. Epoprostenol has a very short half-life (3-5 minutes), and therefore it requires continuous nebulization, rendering it impracticable for long term use. For short-term in-hospital applications, it has advantages over the intravenous route. It can be used for the treatment of an acute crisis of PH, in congenital heart diseases, and in selected perioperative cardiac procedures. The ideal dosing remains unclear, but in 1 study, there was a significant improvement in the oxygenation index at 30 ng/kg/min, and a trend toward significance at doses of 20, 40, and 50 ng/kg/min (LoE B).[68,69]

ILOPROST

It is a prostacyclin analog pharmacologically similar to epoprostenol, with a longer half-life (20-30 minutes), lower viscosity, greater stability, and more physiologic pH, turning it a better choice for nebulization. The longer half-life of iloprost has been associated with an increased risk of arterial hypotension from systemic spillover, leading to the recommendation of intermittent delivery. The administration of iloprost by a vibrating mesh nebulizer (Aerogen®) placed proximal to the Y-piece (inspiratory limb) delivers greater doses than when the nebulizer is placed more distally, near the humidifier. Drug delivery with proximal administration is 3 times greater in high-frequency oscillatory ventilation. The in vitro evidence supports intermittent delivery of iloprost via a proximal vibrating mesh nebulizer during neonatal ventilation. In the acute care setting, doses range from a 0.5 µg/kg/dose to 2 mcg/kg/dose every 30 minutes to 2 hours (6-9 inhalations per day). Iloprost in combination with other pulmonary vasodilators, such as iNO, may be an effective alternative to extracorporeal membrane oxygenation (ECMO) during pulmonary hypertensive crisis (LoE B).[68,70]

TREPROSTINIL

Trepostrinil is a prostacyclin analog to iloprost, with a longer elimination half-life of 4 hours, and a more favorable administration schedule (4 times a day). It also has a lower risk of a rebound PH after abrupt discontinuation. Treprostinil is administered via the Opti-Neb®, a hand-held ultrasonic nebulizer (6 µg/dose). It is possible to deliver aerosolized treprostinil at controlled doses via a mechanical ventilator, respecting heat and humidity of the system, that may affect the aerosol delivery (LoE B).[68,69]

The author's position regarding the treatment of term and near-term (≥34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of persistent PH of the newborn is that iNO is the first-line inhaled therapy. Iloprost in combination with iNO may be an effective alternative to ECMO, and should also be tried in iNO non-responders. The treatment of PH must obey a specific protocol.

ADMINISTRATION OF INHALED VASODILATORS

Clinicians who administer inhaled prostacyclin analogs may not have a clear understanding of its risks, because of the lack of data from large trials examining safety and efficacy. The off-label use (unapproved age group, dosage, or route of administration) of these drugs is legitimate, knowing the limitations and risks, and provided it does not violate ethical guidelines or safety regulations. Although some prostaglandins have been shown to work acutely, their pulmonary vascular selectivity is dependent upon metabolic clearance before they reach the systemic circulation, which is dose-related. Minimizing the systemic effects of absorbed molecules is challenging because of the variation in particle size, the wide variation in the delivered dose, and the excipients used. An apparatus to continuously deliver aerosolized prostacyclin during mechanical ventilation has not been developed. The newer-generation vibrating-mesh micropump nebulizers and the newer-generation prostacyclin analog compounds designed for pulmonary administration can reduce concerns about drug delivery, drug half-life, and pH, and should be considered the actual standard-of-care.[71]

ANTIBIOTICS

Systemic antibiotics utilized in the treatment of multidrug-resistant Gram-negative bacteria-related nosocomial infections and ventilator-associated pneumonia (VAP) are often unsatisfactory, due to the toxicity and suboptimal pulmonary concentrations, making aerosolized antimicrobial agents appealing.

AEROSOLIZED COLISTIN

Colistin proved to be a life-saving drug when used to treat colistin-susceptible multidrug-resistant Gram-negative bacteria-related nosocomial infections and VAP. A few authors

reported its successful use in neonates, with or without concomitant intravenous colistin, in *Acinetobacter baumannii* and *Pseudomonas aeruginosa*-related VAP (LoE C).[72-75]

MUCOLYTICS

Recombinant Human DNase

rhDNase has been shown to be effective as a mucolytic agent in treating neonates with persistent atelectasis who did not respond to other measures (LoE C).[76,77]

Hypertonic Saline (3% NaCl)

Hypertonic saline nebulization may be useful in making secretions less viscous and promoting their excretion, thereby resulting in clinical improvement. Nebulized hypertonic saline has been used in the treatment of atelectasis (LoE C).[78] The role of hypertonic saline in the treatment of acute bronchiolitis has been assessed in a systematic review of 24 trials involving 3209 patients, of whom 1706 received hypertonic saline.[79] Nebulized hypertonic saline reduced the risk of hospitalization by 20% compared with 0.9% saline, and hospitalized patients treated with nebulized hypertonic saline had a significantly shorter length of stay compared with those receiving 0.9% saline or standard care (LoE A). However, hypertonic saline has not been studied in NICU settings.

SURFACTANTS

Calfactant

Exogenous surfactants to treat RDS are approved for tracheal instillation only. This instillation requires intubation, often followed by positive pressure ventilation. In a randomized controlled trial in neonates with early, mild to moderate respiratory distress, aerosolized calfactant at a dose of 210 mg phospholipid/kg body weight reduced intubation and additional surfactant instillation by nearly one-half (LoE B).[80] This is a promising therapy to be used in the future.

CONCLUSION

Respiratory problems, such as RDS, BPD, TTN, acute bronchiolitis, PH, and others, are important causes of NICU admissions. Inhaled pharmacotherapy offers several advantages over the systemic routes. Bronchodilators, epinephrine, corticosteroids, anti-inflammatory agents, pulmonary vasodilators, mucolytics, colistin and, more recently, surfactants, are the most commonly used inhalation agents in neonates. Because of the limited data from studies and the absence of rigorous tests, all these drugs are often used off-label in neonates. They have the advantage of fewer systemic effects, but they have a low evidence of efficacy. We can expect that the future studies on pulmonary vasodilators, in preterm and term neonates, will allow us better and safer use of these off-label agents.

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