How to Deliver Respiratory Treatments to Neonates by Nebulization

Peter R. Morresey, BVSc

Delivery of drugs by aerosol may allow higher concentrations of therapeutic agents to act locally at the site of pulmonary infection or inflammation, and therefore, the potential for systemic side effects is minimized. Aerosolization of therapeutic agents acts as a useful adjunct to more conventional systemic therapies. Author’s address: Rood and Riddle Equine Hospital, PO Box 12070, Lexington, KY 40580; e-mail: pmorresey@roodandriddle.com. © 2008 AAEP.

1. Introduction

Successful treatment of respiratory infection and inflammation can be impaired by the difficulty in achieving therapeutic levels of pulmonary drugs given by the systemic route. Aerosol administration of drugs allows the rapid achievement of high concentrations of therapeutic agents in the pulmonary epithelial lining and bronchiolar fluid. Lower overall doses of the drug are required to achieve therapeutic levels compared with systemic therapies alone. Local delivery can minimize the occurrence of systemic side effects and drug residues. The alteration of respiratory tract secretion viscosity by the administration of mucolytic drugs allows easier removal by clearance mechanisms.

2. Materials and Methods

Mechanics of Aerosol Therapy

An aerosol is a gas containing finely distributed solid or liquid particles in suspension. Properties of the aerosol are governed by both the physical attributes of the individual particles and their collective behavior. Particle size as well as their mass and velocity tend to be highly variable within the aerosol.

Size distribution of particles is the most important determinant of the quantity of inhaled particles that penetrate the tracheobronchial tree to reach the lung. Particles reach different areas of the respiratory tract dependent on their size. As particle size decreases, site of deposition within the respiratory tract becomes deeper. To reach the distal airways, particle sizes \(<5 \mu m\) in diameter are required.\(^1\)

Two different mechanisms exist for the delivery of medications by nebulization: the high-pressure jet nebulizer and the ultrasonic nebulizer. With the jet nebulizer, the aerosol is generated by the flow of compressed gas through the liquid. The primary spray contains a wide range of droplet sizes, and the larger ones strike the wall of the device and drain back for reaperosolization. The smaller droplets are able to exit the device. By altering the airflow entering the nebulizer, the size of aerosolized particles generated, and hence their pulmonary distribution can be altered. The ultrasonic nebulizer uses airflow to carry droplets generated by ultrasonic vibrations. Aerosols can be highly concentrated;
however, at high-flow rates, particle size is greater than those generated by jet nebulizers.²

Ability to deliver aerosolized drugs to equine airways has been shown.³ Although both jet and ultrasonic devices are capable of delivering drugs to the horse by aerosol, the percentage of the dose released reaching the lungs was significantly lower with the ultrasonic nebulizer compared with the jet nebulizer. Peripheral deposition within the airways was also significantly higher with jet nebulization compared with ultrasonic nebulization.³

Drugs Used in Aerosol Therapy

Antimicrobials
High levels of antimicrobials are necessary systematically to achieve therapeutic concentrations in respiratory secretions. This increases the probability of adverse side effects. The usage of both β-lactam and aminoglycoside antimicrobials has been investigated in the horse.⁴,⁵ Both ceftiofur and gentamicin aerosol particle density and size were affected by the antimicrobial concentration of the solution. Optimal combinations of particle size and aerosol density for delivery to the intrathoracic airways of the horse were achieved with gentamicin (50 mg/ml) and ceftiofur (25 mg/ml) solutions.⁴ Compared with IV therapy with gentamicin at 6.6 mg/kg, levels of gentamicin in respiratory secretions were considerably higher after nebulization at 2 mg/kg.⁵ Gentamicin accumulation or respiratory inflammation after repeated aerosol was not found to occur, which suggests that this is a safe procedure for treatment of horses with bacterial infections of the airways.⁵ Ceftiofur sodium (2.2 mg/kg) has recently been shown to achieve high therapeutic levels in respiratory secretions, which are higher than those achieved after systemic administration.⁶

Anti-Inflammatories
Few studies are published regarding the efficacy of inhaled corticosteroids in veterinary medicine, although the benefits of systemic corticosteroids in cases of equine airway diseases are well known.⁷ Differences have also been shown in the efficacy of reducing signs of inflammation between systemically administered corticosteroids and traditional methods.⁸ In human medicine, inhaled corticosteroids have been shown to be highly effective in controlling inflammatory conditions. Furthermore, all act by binding a common glucocorticoid receptor, but the difference between individual compounds is in the propensity to cause systemic side effects.⁹ Many corticosteroid drugs exert a topical effect when deposited in the lungs but are inactivated after gastrointestinal absorption. Corticosteroids have a variety of actions that inhibit inflammation, such as decreasing production and secretion of specific mediators from inflammatory cells and reducing the generation of arachidonic acid metabolites (prostaglandins, leukotrienes). Pulmonary function testing responses and clinical signs of airway obstruction are both improved by administration of inhaled corticosteroids; however, the magnitude of response is dependent on dosage and not necessarily improved over the usage of systemic corticosteroids. Therefore, frequency of treatment and dose rate must be considered when seeking to achieve superior anti-inflammatory responses by aerosol compared with parenterally administered corticosteroids.⁷

Bronchodilators
Sympathomimetic agents (β₂ adrenergic agonists) stimulate receptors on smooth muscle cells of the airway walls, which promotes relaxation of muscle and bronchodilation. More recent drugs have been developed to have more selective binding to respiratory β₂ receptors as well as to have a more prolonged action period.

Inhaled bronchodilators have been shown to be more efficacious than systemic administration of the same compound in their ability to counter bronchoconstriction.¹⁰,¹¹ An increase in mucociliary clearance has also been reported with the use of β₂ adrenergic agonists, because it enhances ciliary activity and facilitates productive coughing by airway dilation.¹² These drugs also stabilize pulmonary mast cells.¹ Pretreatment with β₂ adrenergic agonist bronchodilators is, therefore, a rational course of action to aid in the prevention of medication-associated bronchoconstriction.

Mucolytics
Removal of mucus from the airways depends on viscosity, amount produced, and competency of the clearance mechanisms. Mucolytic drugs decrease the viscosity of mucus to enable more efficient transport up the tracheobronchial tree. Sterile water, sterile saline, and N-acetylcysteine are all shown to decrease the viscosity of mucus and are useful adjuncts to inhalant therapies.¹ Aerosolized medications may induce bronchoconstriction, which suggests that the concurrent use of a bronchodilator may be beneficial.¹

N-Acetylcysteine displays an ability to alter meconium’s physical properties, reducing meconium viscosity by 99% in vitro.¹³ The mechanism of action involves the breakage of disulfide bonds. Because N-acetylcysteine alters protein structure, it may also inactivate digestive enzymes shown to exacerbate pulmonary damage after meconium aspiration.¹³

Equipment for the Practical Application of Aerosol Therapy
Aerosol delivery of medications (Table 1) may be conveniently provided by usage of an in-line (jet) small-volume nebulizer (Fig. 1). Medication is placed within the nebulizer jar, and the device is fitted to a suitable face mask. This can be conveniently and cost effectively achieved by the usage of a large dog-sized anesthetic mask or modification of a plastic 1-gal container (Fig. 2). Alternatively, a
proprietary product such as the foal-sized Aeromask ES\textsuperscript{d} can be used. Oxygen or compressed air-flow rate is set to the nebulizer manufacturer’s recommendation (in this case, 8 l/min).

During nebulization, the foal is supported in sternal recumbency, if unable to rise, or in restrained standing (Fig. 3). This is to ensure maximal ventilation of the lung fields because of minimal impediment to thoracic excursions. This also serves to minimize areas of lung collapse (non-aeration) caused by positioning of the patient.

The 6-ml nebulizer jar is sufficient to contain medications for the neonatal foal. Medication volume can be adjusted up to 6 ml to achieve the desired medication viscosity or antimicrobial concentration by the addition of sterile water or other appropriate liquid for dilution. This has the added benefit of providing moisture to decrease the viscosity of respiratory secretions or aspirated materials such as milk or meconium. The addition of a bronchodilator (albuterol sulfate\textsuperscript{d}) may assist in countering bronchoconstriction stimulated by other drugs. Additionally, ciliary clearance is enhanced by adrenergic stimulation.\textsuperscript{1} The total volume will be nebulized in \textasciitilde 10 min, depending on the viscosity of the solutions used in treatment.

### 3. Results

Drug delivery by nebulization is a useful adjunct to more conventional systemic therapies where diffuse inflammation, direct airway irritation, and significant consolidation of lung parenchyma are present. Aerosol therapy is expensive and time consuming; however, it is safe, and there are few residual effects. Some degree of restraint is necessary with fractious patients; however, care is needed to avoid

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**Table 1. Dosages of Drugs Suitable for Nebulization Therapy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug Description</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobials</td>
<td>Ceftiofur sodium\textsuperscript{a}</td>
<td>1 mg/kg q 6 h (author)</td>
</tr>
<tr>
<td></td>
<td>Gentamicin</td>
<td>2.2 mg/kg q 24 h (Ref. 6)</td>
</tr>
<tr>
<td></td>
<td>2 mg/kg q 24 h (extrapolated from McKenzie\textsuperscript{b} by author)</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatories</td>
<td>Dexamethasone</td>
<td>0.01–0.02 mg/kg q 12–24 h (author)</td>
</tr>
<tr>
<td></td>
<td>Fluticasone</td>
<td>2–4 \mu g/kg q 12–24 h (author)</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Albuterol sulfate\textsuperscript{d}</td>
<td>0.025 mg/kg q 6 h (author)</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>Sterile water</td>
<td>2–5 ml/50 kg q 6 h (Ref. 1)</td>
</tr>
<tr>
<td></td>
<td>Sterile saline</td>
<td>2–5 ml/50 kg q 6 h (Ref. 1)</td>
</tr>
<tr>
<td></td>
<td>N-acetylcysteine 20%\textsuperscript{b}</td>
<td>4–8 mg/kg q 6 h (Ref. 1)</td>
</tr>
</tbody>
</table>

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\textsuperscript{d} Albuterol sulfate.
exacerbating respiratory distress caused by excessive struggling by the patient. Confinement by the mask and the noxious smell of some aerosols (especially N-acetylcysteine) can worsen avoidance reactions by the foal.

Case 1: Meconium Aspiration in a Newborn Foal
A 1-day-old foal was presented after birth because of the rapid onset of depression and respiratory distress. Foaling had been assisted because of previously diagnosed placentitis leading to premature placental separation. Severe meconium staining was reported at birth. On examination, foal respiratory rate and effort were markedly increased, and hypoxemia was present (Table 2). Ultrasonography showed widespread pulmonary pleural irregularities. Thoracic radiographs showed a widespread, diffuse pulmonary interstitial infiltrate. Routine systemic antimicrobial treatment and supportive care were initiated.

Nebulization therapy using an in-line (jet) small-volume nebulizer was started as follows: ceftiofur (1 mg/kg, q 6 h; antimicrobial coverage), dexamethasone (0.01 mg/kg, q 12 h; anti-inflammatory), N-acetylcysteine (4 mg/kg, q 6 h; mucolytic), and albuterol sulfate (0.025 mg/kg, q 6 h; bronchodilation). All treatments were increased to a 6 ml total volume with sterile water (mucolytic). Dexamethasone was decreased to once daily after 48 h. A total of 4 days of aerosol treatment was given.

Respiratory rate and effort were appropriate with hypoxemia resolved at 48 h. Follow-up thoracic radiographs at 5 days showed a marked decrease in the interstitial infiltrate. The foal was discharged on systemic antimicrobials.

Case 2: Milk-Aspiration Pneumonia in a 4-Day-Old Foal
A 4-day-old foal presented after the onset of high fever and the progressive onset of labored breathing. A mild period of depression had occurred on the farm at 48 h of age, and there was development of an intermittent suckle reflex and loss of affinity for the mare. Mild hypoxic ischemic encephalopathy was diagnosed. The foal was supported by bottle feeding of milk and bolus IV fluids. On examination, the foal was depressed with a 104°F fever and increased respiratory rate and effort (Table 2). A white mucoid discharge was present bilaterally at the nares. Auscultation of the lung fields detected crackles and wheezes predominantly on the right side and a loss of air sounds ventrally. Ultrasonography of the lung fields showed consolidation and abscessation of the right cranioventral lung field. An alveolar pattern was present on thoracic radiographs. A transtracheal aspirate recovered Strep- tococcus equi subspecies zooepidemicus. Routine systemic antimicrobial treatment and supportive care were initiated.

Nebulization therapy using an in-line (jet) small-volume nebulizer was begun as follows: ceftiofur (1 mg/kg, q 6 h; antimicrobial coverage) and albuterol sulfate (0.025 mg/kg, q 6 h; bronchodilation). All treatments increased to a 6 ml total volume with sterile water (mucolytic).

Clinical signs of respiratory compromise rapidly improved, and an appropriate respiratory rate was achieved by the second day of treatment. A decreased frequency of treatment on day 3 led to deterioration in respiratory effort; this was resolved when the original treatment schedule was restored.
Abnormal auscultation findings resolved within 72 h. A total of 5 days aerosol treatment was given. The foal was discharged on systemic antimicrobials.

4. Discussion

Advantages and Disadvantages of Aerosol Therapy

The usage of inhalant therapies in companion animals has recently been reviewed. The ability to localize treatments directly to the tracheobronchial tree is the chief advantage of aerosol therapy. Higher local concentrations can be achieved by bypassing gastrointestinal barriers that limit bioavailability and avoiding metabolic inactivation. Therefore, smaller total doses of drug can be used, which minimizes the potential for toxicity. The onset of aerosolized drug action is also more rapid compared with systemic administration.

Disadvantages of aerosol therapy include complicated delivery systems, multiple daily treatments, exposure of operators to the therapeutic agents, degree of hygiene required to ensure avoidance of infectious-agent transmission between patients, and lack of drug penetration through obstructed airways and areas of atelectasis. Aerosolized antimicrobials and mucolytics may be irritating to the airways and induce bronchoconstriction; therefore, they should be administered with bronchodilator therapy.

Clinical Syndromes

Because of the focus of this presentation, discussion of the use of aerosol therapy will be limited to the following conditions of importance to the neonatal foal.

Pneumonia

Bacterial pneumonia has been described as the most common cause of respiratory disease in foals. Bacterial pneumonia can be secondary to sepsis or prolonged recumbency in the devitalized neonate. The most common bacterial organisms associated with pulmonary disease in foals are the same as those responsible for systemic sepsis, primarily Escherichia coli, Streptococcus spp, Klebsiella pneumoniae, Pasteurella spp, and Actinobacillus spp. Less commonly, Salmonella spp, Pseudomonas spp, and Staphylococcus spp are involved. Pneumonia derived from sepsis tends to have a generalized distribution throughout the lung. Additionally, the development of deleterious responses to sepsis (acute lung injury, respiratory distress syndrome) can exacerbate severity of the bacterial disease.

Aspiration of feed material or saliva can also contribute to the development of pneumonia, whether during suckling or iatrogenically during assisted feeding.

The mainstays of infectious respiratory disease treatment are oral and parenteral antimicrobials. However, the low bioavailability of many drugs administered by these routes limits their concentration in the lung parenchyma and distal airways. Aerosol administration may allow higher concentrations of drug to be achieved at the site of infection throughout the dosage interval. Delivery of gentamicin by aerosol caused antibiotic concentrations in equine bronchial fluids to be higher than those obtained after IV administration. Nebulization of gentamicin, kanamycin sulfate, and polymyxin B sulfate have been reported to be effective in foal pneumonia.

Meconium Aspiration

Meconium Aspiration Syndrome (MAS) has been identified as an important cause of neonatal morbidity and mortality. The free fatty acids in meconium displace surfactant, which results in additional atelectasis and decreased lung compliance. Meconium also induces chemical pneumonitis accompanied by alveolar collapse and edema. Type II alveolar cells produce less surfactant, causing an increase in alveolar surface tension and a decrease in compliance. The resulting atelectasis leads to pulmonary vascular constriction, hypoperfusion, and lung-tissue ischemia. Sloughed epithelium, protein, edema, and hyaline membrane formation further contribute to respiratory distress. The result is dysplasia of the respiratory epithelium. Pneumothorax, pneumomediastinum, or interstitial emphysema can result in severe cases. The use of corticosteroids is beneficial. In one human neonatal study of meconium aspiration, there was a statistically significant difference in the duration of stay, duration of oxygen dependence, and radiological clearance between groups receiving aerosolized corticosteroids and controls. The use of steroids was not associated with an increased incidence of sepsis.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Rectal Temperature (°F)</th>
<th>Respiratory Rate (Breaths per Minute) and Effort</th>
<th>PaO₂ mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>97.4</td>
<td>124, gasping</td>
<td>52</td>
</tr>
<tr>
<td>48 h</td>
<td>100.5</td>
<td>56, normal</td>
<td>93</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>104</td>
<td>88, labored</td>
<td>64</td>
</tr>
<tr>
<td>48 h</td>
<td>101.3</td>
<td>62, normal</td>
<td>102</td>
</tr>
</tbody>
</table>
N-acetylcysteine alters meconium’s physical properties by liquefaction. Less viscous and less sticky meconium is easier to mobilize and remove from the tracheobronchial tree. Even if not completely removed from the lung, liquefied meconium is less able to cause mechanical obstruction and a “ball-valve” effect in the airways.4

Although routinely given in cases of equine neonatal meconium aspiration, the usage of antimicrobials routinely in human neonates suffering meconium aspiration without risk factors for sepsis is controversial.24

**Inflammatory Airway Conditions**

The benefits of anti-inflammatory corticosteroid therapies in the treatment of inflammatory pulmonary conditions of the horse are well known.28 Inflammatory syndromes of importance to the neonate include bacterial infection and aspiration of irritant compounds (milk, meconium, particulate irritants, allergens, and noxious gases). Where the potential for sepsis exists, antimicrobial treatment should be used concurrently.

The application of adjunctive aerosol therapies has considerably improved patient welfare and treatment success in many cases of bacterial pneumonia and meconium aspiration at the author’s institution compared with systemic therapies alone. Most notably, respiratory rate and effort both decrease to more normal levels in cases of pulmonary infection and inflammation.

5. Conclusion

The syndromes detailed above can all be expected to derive clinical benefit from the application of aerosol therapies. Control of infection, reduction of inflammation, enhancement of mucociliary clearance, and reduction in viscosity of aspirated meconium are all potential benefits of this technique. Direct delivery of therapeutic drugs more readily enables effective concentrations at the site of action (airways), because it bypasses barriers to absorption and metabolic degradation while having the potential to minimize systemic side effects.

Treatment of pulmonary conditions in neonates can be frustrating to the clinician. In the compromised neonate, prolonged recumbency and generalized debility favor the onset of pulmonary lung changes. Inability to stand and feed unaided or the lack of a normal suckle and swallow reflex all contribute to potential milk aspiration. Although parenteral therapies are favored in situations where the neonate is critically ill, even drugs given by this route are not always able to effectively penetrate to the site of action required or last for a sufficient time to enable a cure.

Although some equipment is required and technical staff needs to be educated on the technique, the benefit cost is in favor of aerosol therapy. In-line nebulizers and portable aerosol compressors are readily and cheaply available from human medical supply companies, and oxygen to provide a gas flow is available in many clinic and ambulatory practice situations. Drugs, because they are commonly used in veterinary practice, have predictable microbial efficacies and reasonable cost.

References and Footnotes


aNaxcel (ceftiofur sodium), Pfizer, New York, NY 10017.

bMucomyst, American Regent, Shirley, NY 11967.

cHudson RCI Micro Mist nebulizer, Teleflex Medical, Research Triangle Park, NC 27709.


eAlbuterol sulfate inhalation solution, USP 0.083%, Nephron Pharmaceuticals, Orlando, FL 32811.