

New Frontiers in Aerosol Delivery During Mechanical Ventilation

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The scientific basis for inhalation therapy in mechanically-ventilated patients is now firmly established. A variety of new devices that deliver drugs to the lung with high efficiency could be employed for drug delivery during mechanical ventilation. Encapsulation of drugs within liposomes could increase the amount of drug delivered, prolong the effect of a dose, and minimize adverse effects. With improved inhalation devices and surfactant formulations, inhaled surfactant could be employed for several indications in mechanically-ventilated patients. Research is unraveling the causes of some disorders that have been poorly understood, and our improved understanding of the causal mechanisms of various respiratory disorders will provide new applications for inhaled therapies. *Key words: aerosol, mechanical ventilation, ventilator, liposomes, surfactant, pulmonary alveolar proteinosis.* [Respir Care 2004;49(6):666–677. © 2004 Daedalus Enterprises]

Introduction

Aerosol science is experiencing a period of tremendous growth; many new and exciting developments have occurred recently, and many more are on the horizon. The

unprecedented growth in new technology for delivering drugs via inhalation has fueled a renewed interest in employing the inhalation route for treatment of respiratory diseases as well as systemic disorders.¹ Novel formulations of therapeutic agents are being developed for pulmonary and systemic diseases. The challenges to aerosol delivery presented by the unique circumstances during mechanical ventilation have been overcome.² And better understanding of the pathogenesis of certain pulmonary dis-

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Table 1. Goals of Aerosol Therapy

High efficiency of drug delivery
Reproducible dosing
Targeted delivery to site of action
Ease of device operation
Short duration of treatment
Minimized risk to patient and clinician
Environmental protection
Cost-effectiveness

orders is presenting new opportunities for inhalable treatments.

Goals of Aerosol Therapy

The goals of aerosol therapy (Table 1) should serve as a guide to future development. Availability of inhalation devices that deliver drugs to the lung with a high efficiency is of paramount importance. High *efficiency* devices not only ensure that a high proportion of the drug placed in the aerosol generator is delivered to the lungs, they also minimize wastage of expensive drugs. *Precision and consistency* of dosing depends on the device, administration technique, ventilator settings,³ and patient-related factors such as the presence and severity of airway disease. For example, matching ventilators and nebulizers may be necessary to standardize the amount of drug delivered.⁴ The *ease of administration* of drugs to mechanically-ventilated patients influences their utilization as well as adherence to treatment. Devices or techniques that are cumbersome, expensive, or require prolonged administration or frequent monitoring are unlikely to find wide application. Other goals of aerosol therapy are to *minimize risk to the patient and providers*. Therapy with aerosolized drugs should not interfere with vital ventilator functions (such as breath sensing), and blockage of expiratory filters must be avoided. *Environmental protection* from chlorofluorocarbons and other propellants and from genetic materials is of increasing concern. In the current climate of cost-containment, therapies that are *cost-effective* are more likely to be used.

Table 2. Inhaled Therapies for Common Conditions Encountered in Adult Patients in the Medical Intensive Care Unit

Diagnosis	Therapy
ARDS	Surfactant, anti-inflammatories
Pneumonia/sepsis	Antibiotics, surfactant?
COPD exacerbation	Bronchodilators, anti-inflammatories
Pulmonary hypertension	Vasodilators
Asthma	Bronchodilators, anti-inflammatories

ARDS = acute respiratory distress syndrome.
COPD = chronic obstructive pulmonary disease.

With those goals in mind, developments in several areas are worthy of mention. Table 2 lists the common diseases encountered among adults in the medical intensive care unit that could be treated with inhaled therapies. Improvements in the design of aerosol-generating devices and drug formulations have made it possible to deliver various therapies effectively via inhalation. There are, therefore, increasing prospects for employing inhaled therapies to treat illnesses common among critically ill patients in the intensive care unit.

New Devices

Vibrating Plate Technology

Several manufacturers have developed aerosol devices that use a vibrating mesh or plate with multiple apertures to produce a liquid aerosol. These manufacturers include Aerogen (Mountain View, California), Omron (Vernon Hills, Illinois), ODEM (Melbourn, United Kingdom), and Pari Respiratory Equipment (Monterey, California). Some common features among these devices are that they generate aerosols with a high fine-particle fraction⁵ and their efficiency of delivering drugs to the respiratory tract is higher than conventional jet or ultrasonic nebulizers.⁵ The aerosol is generated as a fine mist and no internal baffling system is required. Moreover, they are portable, battery-operated (operation with alternating current is optional with some), they efficiently aerosolize solutions and suspensions, and they have minimal residual volume of medication left in the device. Some are breath-actuated, thereby limiting release of aerosolized drug into the ambient air.

The Aeroneb Pro (Aerogen) is designed for use during mechanical ventilation (Fig. 1).⁵ It is connected to the inspiratory limb of the ventilator circuit and generates aerosol continuously, though it can be adapted to generate aerosol only during inspiration. The aerosol generator, which is powered by alternating current or a rechargeable battery pack, consists of a vibrational element and a domed aperture plate (Fig. 2). The aperture plate has about 1,000 tapered holes that are electroformed in a sheet. The wider portion of the hole is toward the medication, and the narrower end is toward the atmosphere. The medication is placed in a reservoir above the domed aperture plate. When electric current is applied, the ceramic vibrational element expands and contracts, causing the domed aperture plate to move upward and downward by a few micrometers, which creates a micro-pump action that extrudes medication through the apertures to produce an aerosol. Particle size, flow rate, and fine-particle fraction are functions of the aperture exit diameter. The plates can be manufactured with different aperture sizes, to optimize delivery of various drugs.

The rate of nebulization with the Aeroneb Pro ranges from 0.3 to 0.6 mL/min, and its nebulization time is generally shorter than conventional nebulizers. Because it does



Fig. 1. The Aeroneb Pro (shown with battery pack) is placed in the inspiratory limb of the ventilator circuit. (Courtesy of Aerogen)

not require any compressed gas flow or high-energy vibration, its operation is relatively quiet. Another advantage is that the volume of solution remaining in the device at the end of treatment (residual volume) is minuscule.⁵ In fact, the device can aerosolize almost down to the very last drop of liquid, compared to 0.3–1.0 mL remaining in conventional jet and ultrasonic nebulizers. The Aeroneb Pro can be employed with drug suspensions, proteins, and peptides. With conventional ultrasonic nebulizers the solution temperature increases during operation because energy is applied to the drug solution, so ultrasonic nebulizers are unsuitable for some agents, especially proteins and peptides, which can be denatured by heating. In contrast, the temperature increase in the Aeroneb Pro is minimized because the energy required for nebulization is applied to the vibrational element rather than to the drug solution or suspension *per se*.⁵ Thus, with the Aeroneb Pro there is negligible risk of denaturing proteins or peptides or of reducing the activity of antibiotics.

Intratracheal Catheter

The intratracheal catheter is another aerosol device for use during mechanical ventilation. The AeroProbe Intracorporeal Nebulizing Catheter (Trudell Medical International, London, Ontario, Canada) has a central lumen, which transmits the liquid to be aerosolized, plus several additional lumens that surround the central lumen and through which compressed gas is forced under high pressure (100 psi) at a variable flow rate (0.1–3 L/min) (Fig. 3). Each lumen extends throughout the length of the catheter. Aerosol can be produced continuously or intermittently (by delivering a pulsed gas flow). The catheter tapers to approximately 0.5 mm in diameter at its distal tip, and at the tip the liquid medication is aerosolized by the pressurized gas. The aerosol particle size depends on the flow rate of the liquid and the pressure and flow rate of the gas. The catheter can be passed into the trachea via an endotracheal tube or through the working channel of a bronchoscope, and its ability to generate an aerosol within the trachea makes it ideal for targeted aerosol therapy within the lung. Various formulations, including surfactant, antibiotics, suspensions, deoxyribonucleic acid, and other solutions can be aerosolized with the catheter. This device has shown promising results in various animal studies.^{6–8}

New Drug Formulations

Developments in aerosol-generation techniques have been matched by innovative formulations to deliver drugs to the lung. Traditionally, inhalable medications have been in the form of powders, solutions, or drug suspensions, with which multiple daily doses are needed to maintain therapeutic effects. New formulations provide controlled drug release that reduces the frequency of drug administration and systemic adverse effects, which could improve patient adherence to treatment. A detailed discussion of the various drug formulations under development is beyond the scope of this review, but liposomal aerosols are briefly discussed below.

Liposome Formulations

Drug encapsulation within liposomes provides extended therapeutic response, because the liposomes have a slow-release “depot” effect, while minimizing adverse effects. Liposomes are closed, concentric, bilayer-membrane vesicles that have an aqueous center surrounded by a phospholipid membrane, somewhat resembling the architecture of a biological cell (Fig. 4). Liposomes are typically a few micrometers in size, but they can also be much smaller (nanometer-size). Each phospholipid has a polar (hydrophilic) “head” group and 2 hydrophobic “tails”. When phospholipid molecules are hydrated under low-shear con-

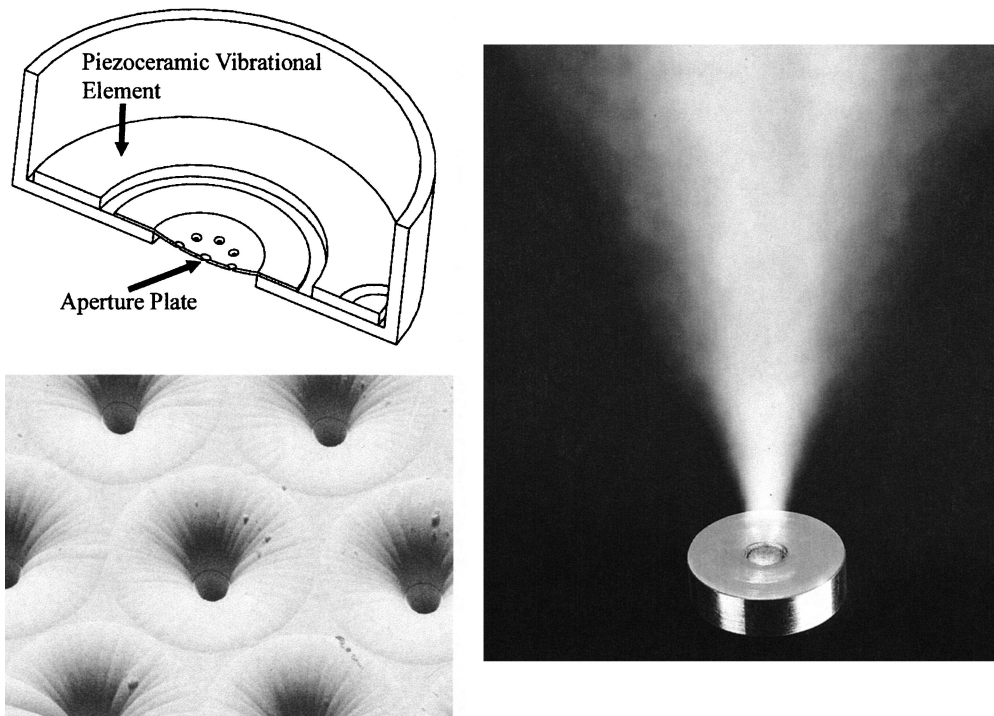


Fig. 2. Aerosol generator of the Aeroneb Pro. The medication is placed in a reservoir above the domed aperture plate, which has approximately 1,000 microscopic, electroformed apertures (lower left), the wider ends of which are toward the medication and the narrower ends toward the atmosphere. When electric current is applied the vibrational element contracts and expands, which extrudes the medication through the apertures. The aerosol has a low velocity because it is not driven by pressurized gas. (From Reference 5)

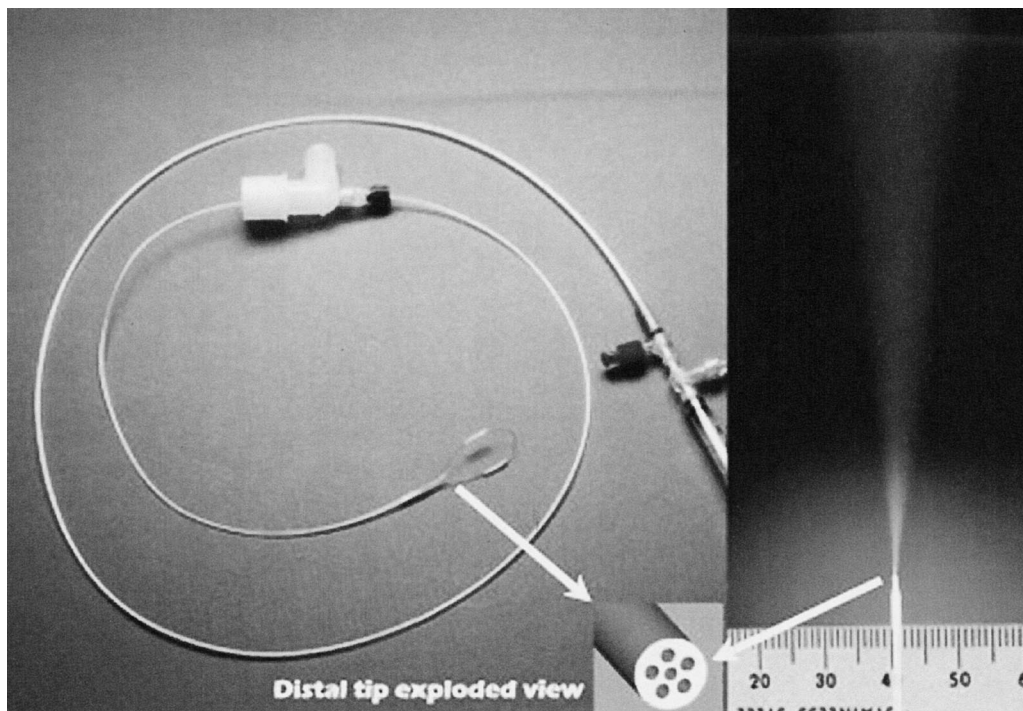


Fig. 3. A multi-lumen catheter designed to produce a fine aerosol within the airway. The catheter can be introduced into the airway through an endotracheal tube or via the working channel of a bronchoscope. The liquid to be aerosolized is delivered through the central lumen, and the aerosol is created by high-pressure jets of air pulsed through the peripheral lumens, at a varying flow rate. (Courtesy of Trudell Medical International)

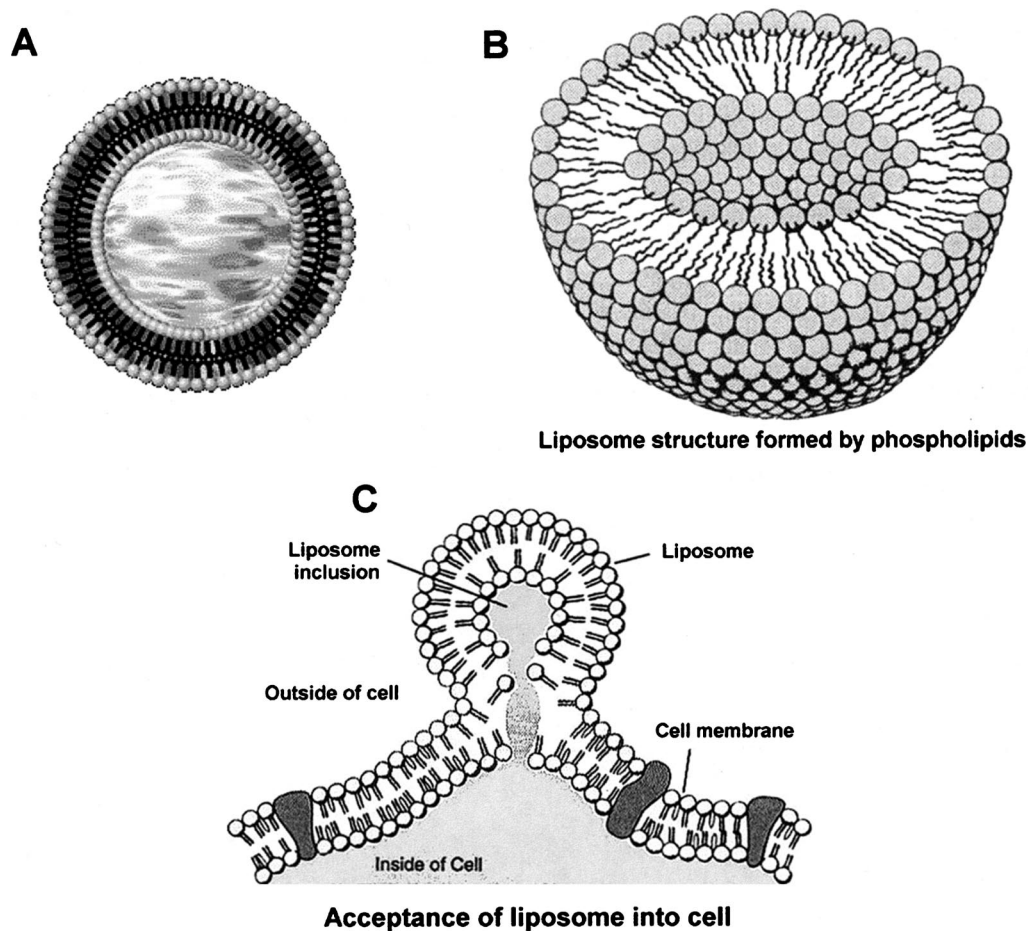


Fig. 4. A: A liposome is a microscopic vesicle that has an aqueous center surrounded by a phospholipid membrane. B: Each phospholipid has a polar (hydrophilic) "head" group and 2 hydrophobic "tails". When phospholipids molecules are hydrated under low-shear conditions, they spontaneously arrange themselves in sheets with their heads up and tails down. These sheets then join tails-to-tails and form a bilayer membrane that encloses water in the center of the sphere. C: The phospholipids in the liposome membrane fuse with the cell membrane and facilitate entry of the encapsulated drug into the interior of the cell.

ditions, they spontaneously arrange in heads-up and tails-down orientation. These phospholipids sheets then join in a tail-to-tail array to form a concentric bilayer membrane that encloses some of the water in an aqueous center (see Fig. 4). During liposome formation water or aqueous solutes are entrapped within the vesicle, whereas lipophilic agents or drugs are encapsulated into the bilayer. Liposomes can be either small and unilamellar or larger multilamellar vesicles. The multilamellar liposomes contain several concentric monolayers of phospholipids, with an onion-like configuration, with alternating bilayers and aqueous compartments. The biophysical properties of liposomes depend on their phospholipid and molecular composition (cholesterol), size, surface charge, and method of preparation.

Liposomes can deliver either hydrophilic (water-soluble) or lipophilic (lipid-soluble) drugs. Water-soluble compounds are carried in the aqueous center, whereas lipophilic drugs are solubilized within the phospholipid

membrane bilayer. Liposomes are high-capacity drug carriers. Because of the similarity between the liposome wall and cell membranes, liposomes merge with cell membranes and facilitate drug delivery to the interior of the cell (see Fig. 4). Cells can also take up small liposomes by phagocytosis.

Liposomes have expanded the potential for more effective use of various inhalable agents. The advantages of liposomes for inhaled therapy are that both hydrophilic and hydrophobic drugs can be selectively delivered via aerosol, adverse effects are minimized, and the duration of drug effect is prolonged. Liposomes could also enhance intracellular delivery of therapeutic agents, including nucleic acids for gene therapy. Liposomal aerosols have proven to be nontoxic in acute human and animal studies.⁹⁻¹¹ In contrast to the rapid clearance of soluble drug from the lung, 50–60% of phosphatidylcholine liposomes are retained in the lung for up to 24 hours after inhalation.^{12,13} In human studies > 80% of an inhaled liposomal

formulation was retained in the lung after 8 hours and 52–73% was retained at 24 hours.^{14,15} For most hydrophobic compounds drug-liposome aerosols could be more effective for lung delivery, deposition, and retention than water-soluble compounds.^{16,17}

Traditionally, jet nebulizers have been employed to administer liposomes, but the high shear stress generated during nebulization can cause liposomes to release their contents.¹⁸ Moreover, impaction of liposomes on the baffles inside the nebulizer can also damage the vesicles and allow drug to leak out. The size of the liposome vesicles, their lipid composition, and the nebulizer's operating conditions also influence the efficiency of liposome delivery.

Waldrep et al estimated lung deposition with various phospholipid liposomes and several different nebulizers.¹¹ Several investigators^{12–15} have studied *in vivo* deposition and clearance of technetium^{99m}-labeled liposomes in healthy volunteers. They found that the type and size of liposome vesicles had less influence on lung deposition than did the characteristics of the aerosol.^{16,17} Lange et al¹⁹ found that the efficiency with which a cationic peptide could be encapsulated and nebulized (with a standard jet nebulizer) was influenced by the phospholipid mixture employed.

Recent advances in nebulizer technology may further expand the use of inhaled liposomes. Aboudan et al did a preliminary study of liposomal albuterol in phosphatidylcholine, in which they aerosolized with a standard jet nebulizer (MicroMist, Hudson, Temecula, California) and an Aeroneb.²⁰ The total drug output from the MicroMist and Aeroneb were comparable with an aqueous albuterol formulation,²⁰ but the liposomal formulation drug output with the Aeroneb was almost twice that from the MicroMist ($p < 0.01$) (Table 3),²⁰ which may be because of the Aeroneb's much lower residual volume. Moreover, the Aeroneb does not require high-pressure gas flow to generate aerosol, so shear stress is probably minimized with the Aeroneb and drug loss from fractured liposomes is therefore probably less.¹⁸ The newer-generation of nebulizers' ability to efficiently aerosolize liposomes greatly expands the potential for clinical application of inhaled therapies.

Surfactant Therapy

Inhaled surfactant therapy has received considerable attention. Endogenous surfactant is a complex mixture of proteins and lipids that line alveolar surfaces and reduce alveolar surface tension, particularly at low lung volumes. Deficiency or dysfunction of endogenous lung surfactant is well known to cause respiratory distress.^{21–23} Surfactant replacement therapy has been evaluated as a treatment for deficiency of endogenous surfactant in neonates and adults with acute lung injury,^{24–26} and it appears promising as a treatment for various other disorders in critically ill pa-

tients,^{27–29} including small-airway diseases (asthma, bronchiolitis), pneumonia, sepsis, and interstitial lung diseases. Many intensive care patients might benefit from surfactant. Currently available artificial surfactants are either mixtures of synthetic phospholipids (eg, Exosurf [Glaxo-SmithKline, United States] and ALEC [Britannia Pharmaceuticals, United Kingdom]) or modified natural surfactants obtained from minced animal lung or alveolar lavage extracts and consisting of phospholipids combined with surfactant proteins B and C (eg, Survanta [Abbott Laboratories, United States], BLES [BLES Biochemicals, Canada], Infasurf [Forest Laboratories, United States], Curosurf [Chiesi Pharmaceuticals, Italy], and Alveofact [Boehringer Ingelheim, Germany]). Newer synthetic surfactants that contain recombinant surfactant protein C (Venticute, Altana, Germany) or a surfactant-protein-B-like peptide (KL-4 surfactant or Surfaxin [Discovery Laboratories, United States]) have also been evaluated in clinical trials.^{30–35} These exogenous surfactants lack surfactant proteins A and D and differ from natural surfactants with respect to their functional and morphologic properties.

Current techniques of exogenous surfactant delivery include liquid bolus instillation through the endotracheal tube, followed by a brief period of manual ventilation.^{24,26} Administration during mechanical ventilation produces a fairly uniform distribution of surfactant within the lung, but that can vary with the administration technique. Bolus delivery of surfactant involves delivering a large volume of fluid into the lung and results in airway pressure elevation and transient oxygen desaturation. In a multicenter study significant oxygenation improvement followed endotracheal instillation of bovine surfactant to mechanically ventilated patients suffering acute respiratory distress syndrome (ARDS).²⁶ Other investigators have employed bronchoscopic surfactant instillation, with favorable results.^{25,36} Bronchoscopic lavage with diluted surfactant via a wedged bronchoscope has the theoretical advantage that it can remove surfactant inhibitors, such as serum proteins and inflammatory cytokines, while the surfactant remains in the lung.³⁷

Surfactant can also be nebulized.^{30–34,38–41} Small quantities of aerosolized surfactant delivered to the parenchyma may be sufficient to lower surface tension and improve lung function.^{32,38} Aerosol delivery of surfactant is easier and safer than instillation, because instillation involves a large-volume bolus of surfactant over a short period to an already compromised lung and also requires changes in the patient's position. However, the viscosity of exogenous surfactants makes them difficult to aerosolize, as they tend to foam and form stable bubbles during nebulization, so lower-respiratory-tract delivery is inefficient and the majority of the aerosol is lost in the delivery system and the ventilator circuit.³⁹ Moreover, exhaled aerosol may deposit in and interfere with valves and monitoring de-

Table 3. Comparison of Aeroneb Versus Jet Nebulizer for Delivery of Aqueous and Liposomal Formulations

Drug Formulation and Nebulizer	MMAD (μm)*	Time of Nebulization (min)	Total Output (μg) (%)	FPF (%)	Estimated Lung Deposition (μg)
<i>Aqueous</i>					
Aeroneb	3.7	1.3	1,807 (72%)	47	535
MicroMist	2.6	6*	1,668 (67%)	52	406
<i>Liposomal</i>					
Aeroneb	3.7	1.8	1,992 (80%)	49	589
MicroMist	2.5*	6†	1,156 (46%)†	65*	273*

MMAD = mass median aerodynamic diameter, determined with an Anderson cascade impactor.

FPF = fine-particle fraction (percent of particles $\leq 3.3 \mu\text{m}$).

*p < 0.05 compared to Aeroneb.

†p < 0.01 compared to Aeroneb.

(Data from Reference 20)

vices, though that can be prevented by placing filters in the expiratory limb.

Aerosolized surfactant administered to animals with non-homogenous lung injury is preferentially deposited in well-ventilated and less-injured lung regions.³¹ Since the pattern of injury in ARDS is not uniform, the more severely affected lung regions may not receive adequate amounts of inhaled surfactant. A few investigators have reported the effects of surfactant administration to mechanically ventilated patients, with conflicting results.^{25,26,30,34,35,40} In a randomized study ARDS patients received saline via nebulizer, surfactant via nebulizer, or surfactant via endotracheal instillation.⁴⁰ With either delivery method surfactant improved oxygenation and there was a trend toward lower mortality in the group that received nebulized surfactant, compared with the group that received nebulized saline. In contrast, 2 prospective multicenter, randomized trials evaluated the efficacy of inhaled surfactant (Exosurf) in sepsis-induced ARDS patients.^{30,34} In these trials Exosurf was nebulized continuously for up to 5 days using an inline large-volume nebulizer that delivered surfactant only during inspiration. In both trials there was no improvement in oxygenation, duration of mechanical ventilation, duration of stay in the intensive care unit, or survival.^{30,34} The absence of a physiologic response was believed to be due to the inefficiency of the delivery device (< 5 mg of the 112 mg/kg body weight dose was estimated to reach the lower airways) and use of a surfactant that lacked proteins.

Recently, investigators evaluated aerosolized surfactant delivery to mechanically-ventilated animals, using different surfactant formulations³³ and an ultrasonic nebulizer.⁴¹ In both studies aerosolized surfactant improved oxygenation in experimental models of acute lung injury.^{33,41}

In summary, aerosolized surfactant could be beneficial in mechanically-ventilated patients, but the current techniques for administering aerosolized surfactant are inefficient. Recent improvements in the design of exogenous

surfactants and delivery systems could facilitate surfactant aerosol administration to ventilator-supported patients.

Changing Paradigms in Disease Management

Newer approaches to treatment develop with better understanding of the etiology and pathogenesis of various disorders. Such newer approaches include drug delivery via inhalation. Pulmonary alveolar proteinosis is a classic example of a disease in which treatment paradigms evolved with improved understanding of the underlying causal mechanisms.

Pulmonary alveolar proteinosis is a rare disorder that is characterized by abnormal accumulation of surfactant in alveoli. The disease was first recognized by Rosen et al in 1958.⁴² Secondary forms of the disease occur in association with hematological cancers, exposure to inorganic dust such as silica, exposure to toxic fumes, following immunosuppressive therapy, or in association with opportunistic infections.⁴³ The primary or idiopathic form of the disease accounts for more than 90% of cases of pulmonary alveolar proteinosis.⁴⁴

The typical patient with a pulmonary alveolar proteinosis is a male smoker (men predominate over women) who is diagnosed with the disease in the fourth decade of life.⁴⁵ Symptoms of cough and gradually progressive exertional dyspnea are usually present for several months before diagnosis.⁴²⁻⁴⁶ Fatigue, weight loss, low-grade fever, chest pain, and hemoptysis occur less commonly. Physical examination is generally unremarkable, except that crackles may be audible on auscultation and clubbing may be present. Laboratory findings are generally normal with the exception that serum lactate dehydrogenase will probably be elevated.⁴⁵ Pulmonary function testing will typically indicate a restrictive pulmonary defect in pulmonary alveolar proteinosis, and the lung's diffusing capacity for carbon monoxide will be disproportionately reduced, relative to

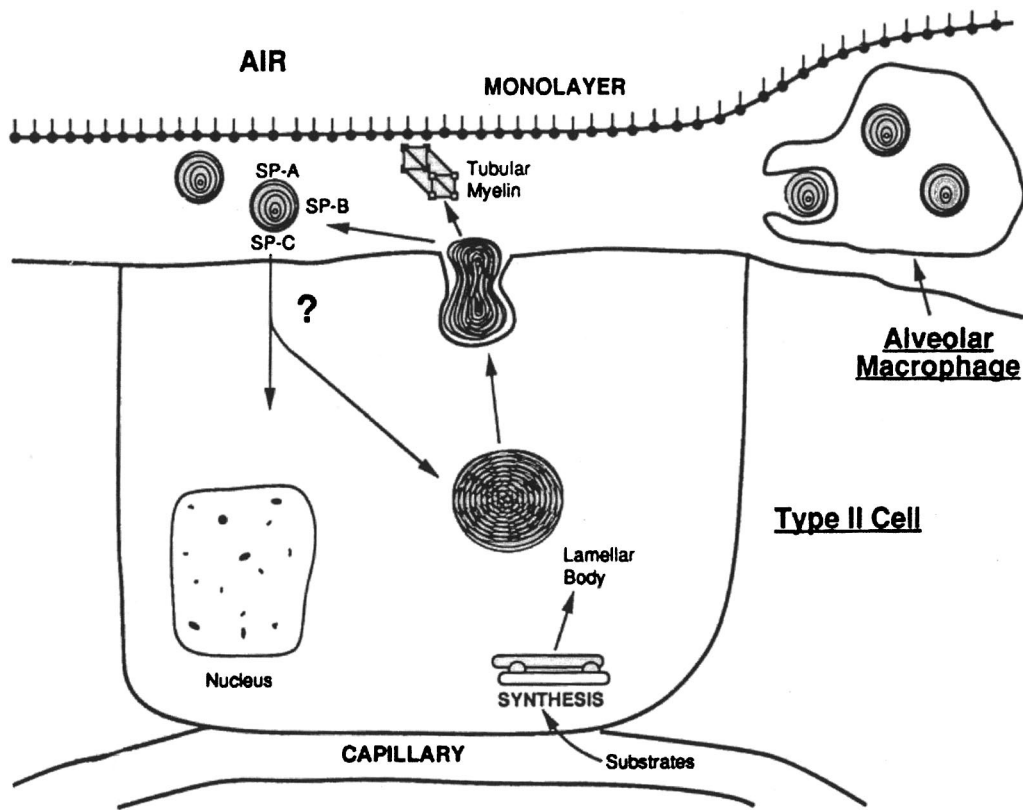


Fig. 5. The life cycle of alveolar surfactant. Surfactant is synthesized and stored within alveolar type II cells, in the form of lamellar bodies, which are secreted into the alveolar space. The functional form of surfactant is a monolayer of phospholipid molecules. Tubular myelin represents a transitional form between recently secreted surfactant and the surface film. Material that leaves the surface film forms unilamellar vesicles that either undergo re-uptake by type II cells or are engulfed by alveolar macrophages. Most of the phospholipids that undergo re-uptake by type II cells are recycled for synthesis of new surfactant. In pulmonary alveolar proteinosis, surfactant clearance is reduced because of defects in alveolar macrophage function, which is believed to lead to surfactant accumulation within alveoli. SP = surfactant protein. (Adapted from Reference 61)

reduced lung volumes. Most pulmonary alveolar proteinosis patients have intrapulmonary shunt that reduces P_{aO_2} and widens the alveolar-arterial oxygen difference.⁴⁵ The chest radiograph generally shows bilateral, patchy, and asymmetrical areas of consolidation.⁴⁷ High-resolution computed tomography shows widespread areas of “ground glass” opacification, with thickening of the interlobular septa, resulting in a “crazy paving” pattern.^{48,49} The bronchoalveolar lavage fluid is milky and includes granular, acellular, eosinophilic, proteinaceous material.⁴⁷ Microscopy typically shows foamy macrophages containing diastase-resistant and positive periodic acid Schiff stain inclusions.⁵⁰ Electron microscopy of the bronchoalveolar lavage fluid characteristically shows structures that resemble lamellar bodies, tubular myelin, and myelin figures.⁵¹ Lung biopsy results typically indicate that the alveoli and terminal bronchioles are filled with positive periodic acid Schiff stain granular eosinophilic material and that the alveolar architecture is preserved, but inflammatory response is generally lacking. For almost 40 years the only available treatment for pulmonary alve-

olar proteinosis was supportive care and whole-lung lavage when necessary.^{52,53} Whole-lung lavage is performed in the operating room under general anesthesia, with adequate control of the airway. The lung is washed with several liters of saline and mechanical ventilation is continued for a few days until the hypoxemia resolves. After whole-lung lavage arterial oxygenation, pulmonary function, radiographic appearance, and alveolar macrophage function improve for a median duration of 15 months, following which the procedure may have to be repeated.⁴⁵ Whole-lung lavage improves survival for pulmonary alveolar proteinosis patients,⁴⁵ although no placebo-controlled, randomized trials have been conducted to confirm its efficacy.

A dramatic turn of events that revolutionized understanding of the pathogenesis of pulmonary alveolar proteinosis occurred in the mid-1990s. An underlying immune disturbance in pulmonary alveolar proteinosis had been suspected for many years. The disease occurs in association with hematological cancers,^{54,55} and patients with primary, acquired pulmonary alveolar proteinosis have a

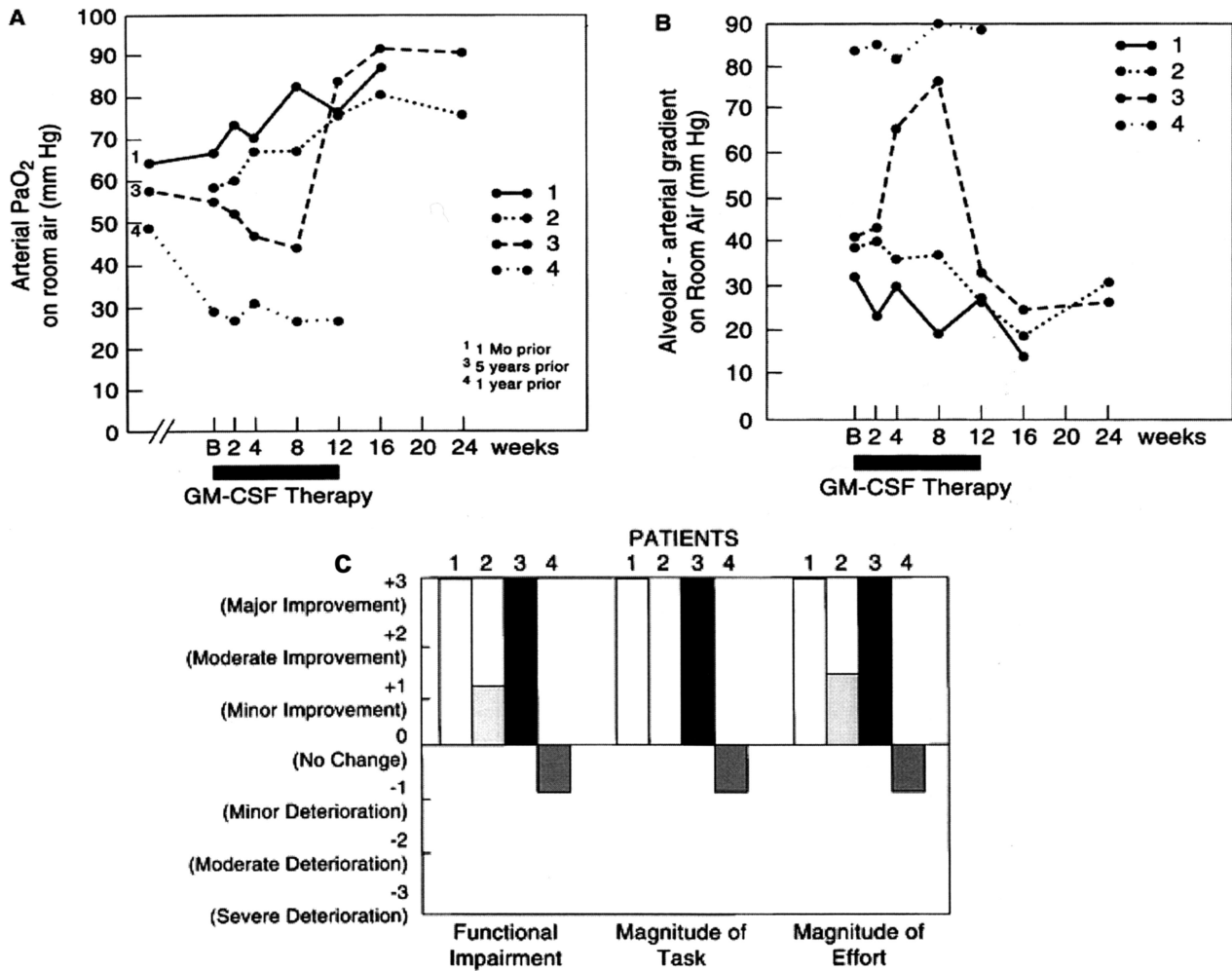


Fig. 6. Effects of granulocyte macrophage colony stimulating factor (GM-CSF) in 4 patients experiencing moderate exacerbations of pulmonary alveolar proteinosis. Escalating doses of GM-CSF were administered subcutaneously for 12 weeks. A: Resting arterial oxygenation while breathing room air. B: Alveolar-arterial oxygen difference while breathing room air. C: Transitional dyspnea index change from baseline. Three of the 4 patients (patients 1, 2, and 3) showed substantial response to GM-CSF. (From Reference 73, with permission)

propensity to develop systemic infections with opportunistic infections such as *Pneumocystis carinii* or *Nocardia*.^{56,57} A major breakthrough occurred with the observation that knockout mice deficient in granulocyte macrophage colony stimulating factor (GM-CSF) developed a pulmonary disorder similar to human pulmonary alveolar proteinosis.^{58,59} The principal abnormality underlying abnormal surfactant accumulation in pulmonary alveolar proteinosis had long been thought to be excessive surfactant production in response to an exogenous irritant. In contrast, in GM-CSF-deficient mice the principal abnormality in surfactant metabolism was due to severe impairment of surfactant clearance from the alveolar space.⁶⁰ Thus, human pulmonary alveolar proteinosis might also be due to defective surfactant clearance from the alveoli. Be-

cause alveolar macrophages are important in surfactant clearance (Fig. 5),⁶¹ their role came under closer scrutiny.

GM-CSF replacement in GM-CSF-deficient mice resolved the abnormal surfactant accumulation.⁶²⁻⁶⁴ Restoration of pulmonary expression of GM-CSF (but not systemic administration) reversed the abnormalities in alveolar macrophage function.⁶² Thus it was realized that, in addition to its role in maturation of hematopoietic cells, GM-CSF is important in stimulating the function of alveolar macrophages.

In humans several molecular mechanisms may explain the development of pulmonary alveolar proteinosis. In infants some cases of congenital alveolar proteinosis are due to heterogeneous mutations of the surfactant protein B or surfactant protein C gene.⁶⁵⁻⁶⁷ Other children have defects

in β c receptor for GM-CSF, interleukin 3, and interleukin 5.⁶⁸ In adults with pulmonary alveolar proteinosis, however, no mutations were found in the GM-CSF genes, GM-CSF receptors, or GM-CSF messenger ribonucleic acid. On the other hand Kitamura et al⁶⁹ reported neutralizing antibodies to GM-CSF in bronchoalveolar lavage fluid and sera from all the adults who had pulmonary alveolar proteinosis but from none of the healthy controls or patients who had other lung diseases.^{69,70} Thus, adult pulmonary alveolar proteinosis may be an autoimmune disorder due to circulating autoantibodies to GM-CSF, and detection of those autoantibodies could be a noninvasive diagnostic test for this disorder.⁷¹

Those revealing studies led to recent trials of GM-CSF in pulmonary alveolar proteinosis. Some adult patients showed dramatic improvement with subcutaneous GM-CSF once daily for 12 weeks.⁷² Fifty percent of the patients showed improved gas exchange after GM-CSF treatment for 4–12 weeks. Most patients who relapsed after treatment was discontinued responded to a second course of treatment. Another group of investigators administered escalating doses of subcutaneous GM-CSF (3–9 μ g/kg/d) once daily for 12 weeks in an open-label trial.⁷³ Three of the 4 patients who were experiencing moderate exacerbations of pulmonary alveolar proteinosis showed symptom-benefit and significant improvement in oxygenation and chest radiographs (Fig. 6).⁷³ GM-CSF may substitute for whole-lung lavage in many pulmonary alveolar proteinosis patients.

Inhaled GM-CSF has also shown favorable results. Because GM-CSF has local antitumor effects, inhaled GM-CSF was initially employed at the Mayo Clinic with patients suffering metastatic cancers.⁷⁴ Escalating doses of inhaled GM-CSF (60–240 μ g/dose twice a day for 7 d) were given, with 1-week intervals between successive doses. Patients tolerated intermittent inhalation of GM-CSF at the highest dose level for 2–6 mo, without adverse effects. The investigators found that inhaled GM-CSF had low toxicity and promising antitumor effects against lung metastasis.⁷⁴ The same group of investigators employed inhaled GM-CSF in a pulmonary alveolar proteinosis patient.⁷⁵ In the preliminary report that patient's pulmonary function improved over 6 months of intermittent therapy (250 μ g twice a day for 7 d on alternating weeks) with no adverse effects.⁷⁵ Thus it appears that inhaled GM-CSF can safely treat pulmonary alveolar proteinosis. Further developments on this subject are awaited with great interest.

Summary

The development of novel aerosol delivery devices has significantly improved the efficiency of drug delivery to mechanically-ventilated patients. The availability of such

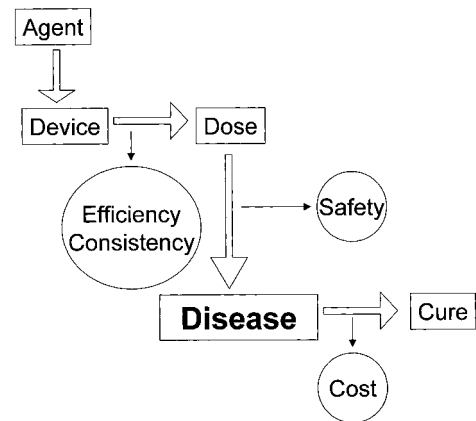


Fig. 7. Flow diagram showing the steps for future development of inhaled therapies. A variety of agents, including antibiotics, prostaglandins, surfactant, anti-inflammatory cytokines, hormones, oligonucleotides, and genes are being investigated for inhalation delivery. Successful therapy will depend on high-efficiency devices that safely and cost-effectively deliver adequate doses to the desired portions of the lung. As we learn the underlying causes of various diseases, treatment objectives will shift from symptom-control to cure. Inhaled drugs will play an important role in future therapy for respiratory disorders.

devices opens up new and exciting possibilities for delivering novel drug formulations via inhalation to mechanically ventilated patients, which will lead to wider application of inhaled therapies with those patients. For a variety of disorders, evolving management paradigms (Fig. 7) have altered the goals of treatment from symptom management to seeking cures. In these new paradigms inhalation therapy could play an increasingly dominant role with various respiratory disorders.

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