Aerosolized Medications-On the Fringe

Everything You used to Know About Aerosolized Medications –But Forgot After Respiratory School
Aerosolized Antimicrobial Therapy

Inhaled antimicrobial therapy is attractive because of its potential to provide high concentrations of antimicrobials to the site of active respiratory infections while avoiding systemic toxicity. In other words "putting the medicine where the problem is" i.e. the lungs!

Many antimicrobials have been used in inhaled preparations, including amino-glycosides, colistin sodium, cephalosporins, penicillins, vancomycin, amphotericin B, and several antiviral compounds.

I'll bet you didn't know about inhaled colistin….that's an interesting one……gaining importance. Before doing research for this little discussion, I had not heard of nebulized Amphotericin B. That's a nasty drug. It would be wonderful to be able to avoid systemic side effects. There's a good reason why we call it "Amphoterrible". But before we can discuss this any further let’s review why aerosolized medications are used and needed in medicine today.

Introduction

The respiratory tract is high on the list of organ systems susceptible to infection by bacteria, fungi, and viruses. As therapists, we know this. **Bacterial pneumonia is the second most common infection in the hospital (with urinary tract infections being the most common)**, and invasive fungal infections such as pulmonary aspergillosis are increasing due to the growing population of immuno-compromised patients alive after stem cell transplantation (HSCT) and solid organ transplantations.

Pulmonary infections in general carry high mortality, significant morbidity, and elevated costs to the health care system. We have also seen this. The mainstay of pulmonary infection treatment is antimicrobial therapy, which is most often administered orally or by IV. **Here's a thought: Is that the best way to do it?**

However, because poor pulmonary absorption is a common characteristic of most systemically administered antimicrobials, inhalation of these drugs has been explored as both preventative and therapeutic approaches for respiratory tract infections.

The direct delivery of antimicrobials by inhalation to the respiratory tract results in local drug concentrations far higher than achievable via enteral or parenteral administration. In addition, direct drug delivery may lead to lower systemic toxicity risk due to lower overall systemic exposure. **Ok,**
we can go along with that fairly well.

Let's get a little bit more specific. Antimicrobials used in inhaled preparations include:

- Aminoglycosides (tobramycin, gentamicin, and amikacin),
- Polymyxins (colistimethate sodium), cephalosporins (ceftazidime, cefotaxime, and cephaloridine),
- Penicillins (ticarcillin, piperacillin, and carbenicillin),
- Vancomycin,
- Polyene antifungals (deoxycholate and lipid formulations),
- Antiviral compounds (ribavirin).

However, the US Food and Drug Administration (FDA) has approved only a few (4) products for inhalation therapy:

1. **Inhaled tobramycin [TOBI]**, which is approved for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*;

   ![](image1.jpg)

   *Many of us are familiar with this one*

2. **Zanamivir for inhalation**, indicated for the prophylaxis and treatment of influenza A and B virus in adults and children;

   ![](image2.jpg)

   *Most of us call this "Flu Mist". I think someone told her that her choice was this or a shot.*
Maybe they didn't tell him.

3. **Pentamidine isethionate for inhalation**, indicated for prophylaxis of *Pneumocystis jiroveci* (formerly *Pneumocystic carinii*) pneumonia (PCP) in AIDS patients;

We've got to give pentamidine carefully. We use a filter. That's easy. *It's been a life saver.*

With the progress in AIDS medications, thank goodness, we don't have to do it as often now.
4. And **ribavirin for inhalation**, indicated for treatment of severe respiratory syncytial virus (RSV) in hospitalized infants and young children.

*The SPAG unit. "small particle aerosol generator" Actually, this was developed by the military. You're right, we don't want to know why. We used this to give Ribavirin to little babies with RSV. It turns out that we probably hurt them more than we helped them. It's bad when we go wrong.*

Recently, interest in inhaled antimicrobial therapy has been renewed because of increasing respiratory infections due to multi-drug-resistant organisms.

That's for sure…MRSA……all over the place

Of course, as far as MRSA is concerned, our infection control practices aren't always that wonderful……..
In recent years, several well-written papers have extensively reviewed the history and mechanics of inhaled antimicrobials. That's a good thing.

**Drug Delivery Considerations for Inhaled Antimicrobials**

Currently, most antimicrobials are administered via a nebulizer; only zanamivir [FluMist] is available as a metered dose inhaler, in which the drug is a dry powder that becomes aerosolized.

A nebulizer that will consistently generate particle sizes in the range of 1 to 5 microns in diameter is required because particles larger than 5 microns are generally deposited in the oropharynx and subsequently swallowed, whereas particles smaller than 1 microns are too small to be deposited in the lung and are eliminated from the body upon exhalation.

*You remember that one from school, right?*

The two most widely used types of nebulizers are jet nebulizers, the ones we use for everyday treatments, and ultrasonic nebulizers.

Although each nebulizer type may generate particles of appropriate size, jet nebulizers may be better suited for use with inhaled antimicrobials, because they do not require the drug to be heated, thereby avoiding the risk of degradation. More recently, significant advances have been made in dry powder administration techniques, which appear to demonstrate improved drug delivery to the lung.

Probably we will use a combination of ordinary small volume nebulizers (SVNs) [they are improving, though slowly], dry powder, and mesh nebulizer technology, as we see with, for example, the Aerogen.

Importantly, intravenous (IV) antimicrobial formulations are not intended for aerosol administration, thereby, often, resulting in poor tolerability when inhaled. Factors such as isotonicity, pH, presence of preservatives, and toxic metabolites must be considered when evaluating a drug for potential administration via inhalation.

For example, the FDA issued a public health advisory regarding the use of inhaled colistimethate [colistin] after the death of a CF patient from what appeared to be systemic colistin toxicity. In this particular situation, the patient was prescribed aerosolized colistimethate to be administered at home. The patient received premixed colistimethate from the pharmacy and developed respiratory distress soon after the first dose. This progressed with subsequent doses, and the patient died of multi-system organ failure 19 days later.

When mixed with sterile water for inhalation, colistimethate undergoes spontaneous hydrolysis to two different forms of active drug (polymyxin E1 and E2); polymyxin E2 is toxic to lung
tissue and can potentially cause sufficient damage to allow systemic absorption and toxicity. Because this patient received a premixed supply of colistimethate sodium (more than 24 hours ahead of time), the patient was exposed to a higher than normal concentration of the toxic metabolite.

Therefore, inhaled colistimethate must be administered immediately after mixing to minimize risk of toxicity!

OK, we've got to be careful with this stuff. Being careful is always good.

[Note: Colistin is an old drug that is regaining popularity. It is often effective against resistant pseudomonas aeruginosa. It is also very effective against resistant acinetobacter baumannii. That's a little nasty bug that's been rearing it's ugly head lately. We're beginning to see some old antibiotics coming back to attack some of the new bugs. Seems like some of these new bugs have forgotten how to fight the old guys.]

In addition to important considerations for stability and tolerability of non–FDA-approved solutions for inhalation, other factors can determine the clinical effectiveness of aerosolized antimicrobials.
First, inhalation is at best an inefficient method of administering antimicrobials; only about 10% of the dose is actually deposited in the lungs. We know that from school. The remainder is swallowed, detained in the administration system, or lost to the environment. As a result, significant variability has been reported with respect to the amount of drug delivered to patients.

Geller et al. reported a huge difference in sputum drug concentrations among CF patients administered tobramycin via inhalation using a single nebulizer/compressor combination.

**Despite this variability, high concentrations of antibiotics — often 100- to 1000-fold greater than the minimum inhibitory concentration — can be achieved in the lung. That's a good thing.**

However, pharmacokinetic data may be affected by many patient-specific factors such as tidal breath, respiratory rate, pretreatment with bronchodilators, or the presence of mucus or inflammation.

Clinicians should also be concerned that the drug may not be equally distributed throughout the lung fields, especially in patients with significant lung pathology or anatomic abnormalities. Additionally, even though reduced systemic exposure is a potential benefit from this method of drug delivery, it can also be a liability.

Because systemic levels are low, patients are at risk for secondary infections or non-pulmonary infections if an inhaled antibiotic is used alone.

**We have to watch for that.**

**Cystic Fibrosis**

Inhaled antibiotics can be administered to prevent or treat bacterial infections in patients.

The majority of data pertaining to aerosolized antibiotics has been generated in the CF population, because these patients are at significant risk for recurring acute exacerbations of their chronic infection.

**The use of inhaled tobramycin or colistimethate sodium in CF patients has been shown to:**
- Improve lung function
- Decrease hospitalization rates
- Decrease the use of IV antibiotics.

The most substantial data demonstrating this finding were from two multi-center, double-blind, placebo-controlled trials [in other words, good ones] of intermittent inhaled tobramycin in patients with CF and *P. aeruginosa* infection. A total of 520 patients received 300 mg inhaled tobramycin or placebo twice daily for 4 weeks, followed by 4 weeks with no drug. The cycle was continued for 24 weeks.
Tobramycin-treated patients had an average increase in forced expiratory volume in 1 second (FEV₁) of 10% at week 20 compared with week 0, whereas placebo patients had a 2% decline. Patients receiving tobramycin had their *P. aeruginosa* density decreased by quite a bit and were 26% less likely to be hospitalized than those in the placebo group.

Those are very good numbers. That's why we have FDA approved "TOBI".

More recently, an observation study of inhaled tobramycin after 2 years of maintenance therapy in 12 children and adolescents with CF found sustaining results. Although the study was small and observational, the investigators observed a FEV₁ improvement of 1.5% over the 2 years compared to -7.6% at baseline. Investigators also noted significant improvements in body mass index (*P* = 0.02) and a delay in progression of pulmonary radiography changes.

In Europe, nebulized colistin is also commonly used for the treatment of CF patients chronically infected with *P. aeruginosa*. A recently published study compared the efficacy and safety of inhaled tobramycin versus inhaled colistin in 115 patients. Although patients who were randomized to receive inhaled tobramycin observed a 6.7% improvement in FEV₁ after 1 month, the colistin patients had no improvement. Lung function was also significantly improved over that of colistin-treated patients. These data suggest that inhaled tobramycin might offer an advantage over inhaled colistin for chronic treatment of patients with CF.

Alright, we know that TOBI works. That's good.

Unfortunately, the published study only offered results after 1 month of treatment, and inhaled colistin could have beneficial effects after longer courses. A new formulation of colistin as a dry powder for inhalation is under investigation and may also serve to improve the tolerability of this drug via inhalation because it is known to cause bronchospasm and acutely decrease FEV₁.

So, Colistin might not be good for our CF folks. We're not sure yet.

We certainly need to keep studying the benefit of other aerosolized antibiotics for our CF patients. TOBI has helped them a great deal. We'll need others.

*This girl has CF. She's got a look on her face that no girl her age should have to have. We can't take that away. But, maybe, we can help make sure that the pneumonia she gets next week is one we can beat.*
Ventilator Associated Pneumonia

For several decades, aerosolized antibiotics have been studied in both the prevention and treatment of ventilator associated pneumonia (VAP), and much of this data has been reviewed in previous manuscripts. In these settings, numerous antibiotics have been administered via inhalation, including aminoglycosides, vancomycin, colistin, and C-lactams.

A very well controlled trial by Wood et al. evaluated the safety and efficacy of aerosolized ceftazidime for prevention of VAP.

[Note: ceftazidime is a nice little third generation cephalosporin very effective against gram negative organisms and, most notably, pseudomonas aeruginosa. A very effective antibiotic.]

Forty critically ill trauma patients from a single intensive care unit (ICU) were randomly assigned within 48 hours of ICU admission to aerosolized ceftazidime, 250 mg every 12 hours, or placebo for up to 7 days.

At ICU day 14, the frequency of VAP was 15% in ceftazidime-treated patients and 55% in patients receiving placebo. That's nice. Very, very nice.

The prophylactic use of ceftazidime did not alter the sensitivity patterns in the ICU. Additionally, pulmonary tumor necrosis factor-B, interleukin-C, and interleukin-8 concentrations were significantly lower in the ceftazidime group compared with placebo.

Unfortunately, another study showed poor results. Yet other studies with ceftazidime were either poorly designed, or had very small sample sizes.

So, we don't have enough science behind us yet for preventive use of aerosolized antibiotics for VAP. But, there are quite a few folks still working on that one. I'm glad of that.
We don't have enough data recommend using this approach as a preventive measure, but treatment of VAP itself with inhaled antibiotics when administered along with IV agents may very well have a role, particularly given the significant rise in multi-drug resistant gram-negative and gram-positive bacteria in contemporary ICUs.

Brown et al. published a placebo-controlled study using endotracheal tobramycin as an adjunct to IV antibiotics. They reported bacterial eradication in 56% of patients treated with tobramycin compared with 24% receiving placebo. Aerosolized colistin also demonstrated promising results as supplementary therapy to conventional IV antibiotic treatment for nosocomial pneumonia caused by multi-drug resistant gram-negative microorganisms. *Nice.*

Several observational case series studied inhaled antibiotics for treating VAP, typically in patients with highly resistant organisms or who did not respond to systemic therapy alone. *Based on these reports, the current American Thoracic Society and Infectious Diseases Society of America guidelines for the treatment of nosocomial pneumonia (including VAP) allow the addition of aerosolized antibiotics in select patients with multi-drug resistant gram-negative organisms.* This guideline seems reasonable because of the lack of therapeutic options in such patients.

So, there's a big piece of ammunition to take to your physicians, if they are reluctant to do this. And, as we know, we are seeing more and more resistant pneumonias.

*American Thoracic Society and Infectious Diseases Society of America. That's two big guns. Pictured here is the ATA, I think.*

Inhaled vancomycin is attractive because of the difficulty in treating methicillin-resistant *Staphylococcus aureus* (MRSA) lung infections. However, the only available data include a case report of successful treatment for chronic MRSA infection in a 10-year-old CF patient and eradication of MRSA colonization in children with bronchopulmonary dysplasia and in elderly patients.

**Personal Story / Experience**

It is the administration of vancomycin which renewed my interest in aerosolized antibiotics.
While I was a department director at an acute long term care facility, I managed to convince the Medical Executive Committee to allow me to institute a policy involving nebulized vancomycin. We got all of the patients in the region who couldn't be weaned from the ventilator. They weren't being weaned properly, but that's another story for another article. At any rate, we had MANY ventilator patients…and many of them came to us with MRSA. We gave them a bronchodilator Tx first, and then, using a separate SVN, gave 120mg of vancomycin Q6. They got well. They got well fast. They barely had measurable blood levels of vancomycin. Their kidneys didn't get hurt from the vancomycin. No side effects. Magic. Even though our Director of Pharmacy kept pushing me to do a study, I was too lazy to take it on.

Yes, I failed. This is me, by the way. Well, maybe not.

That's the only honest way to characterize it. At that time, years ago, he had done a literature search and found NOTHING on the subject. I, perhaps, could have gotten some good science for us to use. We've all seen things at the bedside which "work". Use my mistake as a lesson. Get a study going. You know what works. I fact, it was this adventure, or misadventure, which drove me to write this little group of articles.

Back to the movie, now.....

On the research front, one pharmaceutical company is developing a specially formulated, preservative-free preparation of amikacin, which is designed for inhaled administration. The drug is delivered via the company’s proprietary pulmonary drug delivery system directly to the lungs of intubated and mechanically vented patients. Phase 2 studies observed high concentrations of amikacin in both tracheal aspirates and epithelial lining fluid after administration in infected patients.
The drug appeared to be safe, well-tolerated, and associated with less IV antibiotic use compared with placebo. Further clinical trials are underway.

That's good. This is important. Somebody important must think aerosolized amikacin will work. I'll just bet they're right.

**Aerosolized Antifungals**

Invasive fungal infections are a rising concern in severely immuno-compromised patients. Fungal infections in the lung are most often due to Aspergillus, but other non-Aspergillus molds such as Mucor can also cause pulmonary infections. Patients undergoing lung transplantation and bone marrow replacement appear to be at the greatest risk of developing invasive mold infections. Invasive aspergillosis occurs in 3.5% of patients after lung transplantation and 2.9% of those receiving bone marrow replacements.

*Aspergillosis. Aspergillus pneumonia, bilateral, in a 16-year-old boy with acute myelogenous leukemia. Much worse in the right lung, as we see.*

More importantly, mortality due to invasive aspergillosis can exceed 80%, particularly in those receiving bone marrow transplant.

Due to the poor outcomes associated with such infections, their prevention is a common strategy in high-risk patients. Most often, preventive treatment is accomplished with IV or oral antifungal
agents, but interest in aerosolized administration has now expanded to antifungals to target the infection site while minimizing systemic toxicity. Oh yes.

In fact, a recent survey observed that 61% of lung transplantation centers used some form of aerosolized amphotericin B in their invasive fungal infection prevention or treatment protocols.

Most data on aerosolized antifungals involve amphotericin B. Earlier studies with aerosolized amphotericin B for the prevention of fungal infections have been conducted in patients with neutropenia secondary to cancer chemotherapy, bone marrow recipients, or solid organ transplant recipients. Collectively, these studies and others have found small reductions (generally < 25%) in the incidence of invasive fungal infections when compared with control groups.

It was found that aerosolized amphotericin B deoxycholate [we'll call this "conventional amphotericin B"] can be safely delivered to patients and was generally well tolerated at aerosolized doses ranging from 5 to 30 mg once to three times daily. Associated adverse events include nausea, dysphagia, coughing, dyspnea, and bronchospasm, which occurred with great variability (8.5%–69%) in the reported studies. Lastly, administration of aerosolized conventional amphotericin B provides some logistic difficulties; the product is light sensitive and is also known to foam in the nebulizer.

In light of the difficulties administering conventional amphotericin B by inhalation, along with its variability in lung concentrations, lipid formulations of amphotericin B have been explored and found to have several advantages over conventional amphotericin B when aerosolized. First, infection models of aspergillosis have observed greater pulmonary amphotericin B concentrations with the lipid versus the conventional formulation, as well as reduced aspergillus infections when administered prophylactically to rats. Second, lipid formations of amphotericin B tend to be equivalent or better tolerated in patients after lung transplantation than conventional amphotericin B when aerosolized.

So, this lipid formulation seems to work well when nebulized. That's good.

In one double-blind study, treatment-limiting adverse events occurred in 12.2% and 5.9% of patients receiving conventional amphotericin B and lipid complex amphotericin B, respectively.

Lipid complex amphotericin B was also well tolerated in patients with bone marrow transplant after 13 weeks of aerosolized treatment. Cough, nausea, taste disturbance, or vomiting occurred after only 2.2% of 458 total inhaled lipid complex amphotericin B administrations among 40 subjects.

Nice.
Sixteen subjects experienced a 20% or greater decrease in their FEV₁ or forced vital capacity at least once during administration; however, none discontinued therapy or required bronchodilator therapy. Lastly, lipid formulations are less likely to foam in the nebulizer because they are already in solution.

There have been several studies showing good results with preventive treatments for lung transplant patients. In a recent study, only one of 40 patients undergoing bone marrow transplant after receiving treatment with the inhaled lipid form, in combination with oral or IV therapy, had a documented invasive fungal infection while receiving preventive therapy.

Very nice.

Data is limited regarding inhalation of other antifungals, although there are a few reports out there. I won't bother you with those.

So, the science is sparse, but the studies that have been done are promising. Believe me, any patient who has a fungal lung infection needs every single bit of help we can give him or her. You don't get an infection like that unless you're already in trouble.

Would I give an amphotericin SVN Tx to a chemotherapy patient with aspergillosis? You bet I would. I've seen the nasty list of side effects from IV amphotericin. Any way to treat these folks and lessen those side effects is a wonderful thing, indeed.

Here's a little summary of where we sit now in terms of aerosolized antimicrobials:

Table 1. Indications for inhaled antimicrobial therapies for respiratory infections

<table>
<thead>
<tr>
<th>Proven beneficial effects</th>
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<tbody>
<tr>
<td>Inhaled tobramycin (300 mg twice a day every other month) for patients 6 years or older with stable CF colonized with <em>Pseudomonas aeruginosa</em> and an FEV₁ between 25% and 75% of predicted</td>
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<tr>
<td>Monthly aerosolized pentamidine (300 mg every month) for PCP prophylaxis in patients with trimethoprim/sulfamethoxazole or dapsone intolerance and a CD4 count less than 200 cells/mm³</td>
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<tr>
<td>Inhaled zanamivir (10 mg twice a day for 5 days) against influenza A and B within 48 hours of the start of symptoms</td>
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<thead>
<tr>
<th>Probable beneficial effects</th>
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<tr>
<td>Aerosolized tobramycin as an adjunct to parenteral antibiotics or as a sole agent to treat CF exacerbations</td>
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<tr>
<td>Inhaled colistin as chronic suppressive therapy or to change the sensitivity pattern in patients with CF</td>
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<tr>
<td>Inhaled aminoglycosides as chronic immunosuppressive for patients with non-CF bronchiectasis or tracheobronchitis</td>
</tr>
<tr>
<td>Inhaled colistin as an adjunct to parenteral antibiotics to treat multidrug-resistant nosocomial pneumonia</td>
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<tr>
<td>Inhaled ribavirin for RSV infection of the lower respiratory tract in infants and young children</td>
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<tr>
<th>Highly controversial but potentially beneficial effects</th>
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<tr>
<td>Inhaled antibiotics for VAP prophylaxis</td>
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<tr>
<td>Inhaled aminoglycosides as an adjunct to parenteral antibiotics for VAP treatment</td>
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<tr>
<td>Inhaled colistin as an adjunct to parenteral antibiotics to treat multidrug-resistant nosocomial pneumonia</td>
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<tr>
<td>Inhaled amphotericin B for invasive aspergillosis treatment or prophylaxis</td>
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<tr>
<td>Inhaled ribavirin for RSV upper respiratory tract infection in hematopoietic cell transplant recipients</td>
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<tr>
<td>Inhaled aminoglycosides as adjunctive antimycobacterial therapy</td>
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<tr>
<td>Inhaled vancomycin as an adjunct to treat MRSA lung infection</td>
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<tr>
<td>Inhaled zanamivir for prophylaxis against influenza A and B in exposed high-risk individuals</td>
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</tbody>
</table>
Don't worry, we're almost done.

**Aerosolized Pentamidine**

Inhaled pentamidine has been effective in numerous studies for the treatment and prevention of PCP (pneumocystis carinii, now called p. jiroveci) in AIDS patients. We know that. It has been tried for prevention of PCP in bone marrow recipients, with conflicting results, mostly bad. Current use of aerosolized pentamidine is primarily limited to patients who need pneumocystis prevention and cannot tolerate first-line therapies such as trimethoprim-sulfamethoxazole (TMP-SMZ) or dapsone. There are no recent updates in this area. There have been some negative studies about other uses, so this only occupies a small niche now. Still an important niche, though.

*Aerosolized Antivirals*

RSV is one of the most common causes of childhood respiratory tract infections. Although the majority of patients have a self-limited clinical course, a small proportion of children have progressive symptoms resulting in respiratory failure and require mechanical ventilation in addition to basic supportive care.

Recently, a Cochrane review reported that the cumulative results of three small trials using aerosolized ribavirin for RSV infection of the lower respiratory tract in infants and young children showed that ribavirin may reduce the duration of mechanical ventilation and may reduce days of hospitalization.

Based on these strong findings, the investigators suggested performing a large randomized controlled trial of ribavirin for ventilated and other high-risk participants. Severe RSV pneumonia can also occur in adults, particularly in the elderly with co-morbidities or compromised immune status. However, proof of efficacy in adults remains controversial.

So, it looks like, for our really sick folks with RSV, we can still help with this. We should remember that. Maybe those pediatric therapists among us should make sure we can pull ribavirin out of our pockets on those rare occasions.

Zanamivir [Flu Mist] is an orally inhaled competitive inhibitor neuraminidase that blocks the release of the influenza virus from infected cells and is effective against influenza A and B.
Inhaled zanamivir is effective in ameliorating experimental influenza in healthy adults and in community-based epidemics.

Zanamivir has also demonstrated potential for prevention in persons for whom vaccination is contraindicated or ineffective, in elderly or high-risk patients in long-term care facilities and in households; however, it is not currently approved by the FDA for this purpose. That will come, I would predict.

**Conclusions**

Well-designed clinical trials to justify the routine use of inhaled antimicrobials, antifungals, and antivirals are relatively sparse; therefore, this approach can only be recommended based on evidence in a few clinical situations. Stable CF patients with *P. aeruginosa* demonstrated improved pulmonary function and used less parenteral antibiotic therapy if treated with intermittent inhaled tobramycin.

AIDS patients have fewer episodes of *P. jiroveci* with monthly inhaled pentamidine treatments.

Healthy individuals and patients at risk for severe influenza illness can benefit from inhaled zanamivir. [Flu-Mist]

OK, these three things are old news:

![WOW! Old news is so exciting!](image)

Actually, most old news isn't exciting. But these three bits still are.

1. The flu is nasty. I've had it. I wanted to die. My hair hurt. Let alone the fact that the flu kills people. Flu-Mist helps.
2. AIDS patients don't need to die from Pneumocystis. They just don't. Let's stay up with the times now. It's not pneumocystis carinii anymore, it's pneumocystis jiroveci. Bummer. I just learned how to pronounce carinii.

3. CF patients need all the help they can get. Thank goodness for TOBI.

Inhaled antibiotic therapy for the prevention and treatment of VAP has become an area of interest due to the emergence of multi-drug-resistant pathogens; however, no large randomized clinical trials support this use. Current data suggest that inhaled antibiotics may be worthy in the prophylaxis and therapy of VAP. Large, randomized clinical trials are needed to better define the role of inhaled antimicrobials for the prophylaxis and therapy of VAP and to evaluate other controversial areas of inhalation therapy.

As always, we need more studies. That's nothing new.

Inhaled lipid formulations of amphotericin B show promise in preventing mold infections in high-risk patients after lung transplantation.

Inhaled aminoglycosides [the 'mycins'] have shown promise. As have cephalosporins and penicillins. Inhaled colistin is gaining interest. There's a lot going on in this arena. We'll keep our eyes on this.

We can do a lot more than give albuterol, Atrovent, Xopenex, and a little Mucomyst here and there. For our patients with pulmonary infections, let's put some medicine "right where the problem is".

Referring back to our little table above, we see quite a few roles for fighting infection with aerosol.

As for me, I'm excited about attacking MRSA with inhaled vancomycin. Until VRSA takes over, that is.

So, we see that aerosolized antimicrobial therapy, once the "black rose" of aerosol therapy, is slowly turning red…..
Aerosolized Chemotherapy?

These upcoming two little paragraphs say a few big things which have dire implications for a lot of patients:

Lungs are a common site for both primary and secondary tumors. In the United States, 170,000 new cases of primary lung cancer and 65,000 new cases of metastatic lung cancer are diagnosed each year. Non small-cell lung cancer [NSCLC] is diagnosed in 80% of primary tumors. Metastatic lung cancer is frequently detected in patients with lung, breast, colorectal, pancreatic, gastric, kidney, and head and neck carcinomas, and melanoma.

Lung carcinoma is the leading cause of cancer-related deaths worldwide. Only a minority of patients with primary lung cancer are eligible for curative surgical resection.

Similarly, surgical treatment of lung metastasis is often contraindicated due to the number or the site of the lesions and the patient’s respiratory and/or general status. Chemotherapy is therefore widely used in both primary and secondary lung carcinomas. Despite the use of new chemotherapeutic agents during the last decade, the ceiling of their clinical efficacy remains low with a 5-year survival rate of metastatic NSCLC that levels off at 5–15%.

As bad as those statistics are, they are worse for "small cell" cancer, also called "oat cell" lung cancer. And, of course, the prognosis in metastatic lung cancer is, almost invariably, death.

Studies have demonstrated that drug concentrations in lung tumors are low after systemic administration; that could be a cause of treatment failure, as the drug concentration in the tumor appears to be a key parameter to achieve drug efficacy in humans. This information supports the potential value of targeted chemotherapy to lung tumors, as already successfully applied in several cancer settings such as liver metastasis, ovarian tumors, and neoplastic meningitis or brain tumors.

So, we've already seen that targeted chemotherapy, in other words "putting the medicine where the cancer is" does work.

I've long been attracted to the idea of treating the lungs locally, with aerosolized medications. I'm talking outside of the world of the old albuterol treatment, here. The typical practice of prescribing bronchodilators is another discussion, which we should have. I've seen breathing treatments prescribed for everything from headaches to bunions. I'm surprised they don't nebulize albuterol through the hospital's air conditioning ducts……
I have personally seen some wonderful results at the bedside involving aerosolization of antibiotics, aerosolization of morphine, and even nebulized mucolytics, though some therapists might not want to believe me on that last one.

So, given that, this subject of aerosolization of chemotherapy drugs garnered my interest quickly. I looked around and found that I was not alone.

So, let's see what science we have to lean on here…

Science is always a good shoulder to lean on. Wait, if I were that little boy, I don't think I would like that sculpture. No, I'm sure I wouldn't.

Rationale and Potential Limitations of Aerosolized Chemotherapy in Lung Cancer

Direct drug administration to the lungs via inhalation offers several theoretical advantages over systemic delivery, including the possibility of regional drug delivery to the lungs and airways with lower doses and fewer systemic side effects, avoiding first-pass metabolism of the drug in the liver and the use of a noninvasive “needle-free” delivery system. The alveolar surface also provides a large surface area for rapid systemic absorption of soluble drugs. The most common application of aerosol therapy is regional drug delivery for airway and parenchymal lung diseases, but there is also an expanding role of aerosols in systemic drug delivery such as insulin for diabetes.

Local delivery of chemotherapy via inhalation for primary or metastatic lung cancer could increase drug exposure of the lung tumor, while minimizing systemic side effects.

[I think many of us have seen the horrible side effects seen with chemotherapy with our cancer patients. Let me just give you the short list for cisplatin, a very commonly prescribed chemotherapy agent: kidney damage, nerve damage, nausea and vomiting, severe electrolyte disturbances, alopecia, and hearing loss, to name a few]
Although use of aerosolized chemotherapy was first reported in 1968 [can you believe that?], the development of inhalational agents for oncologic use has been limited. A potential explanation is the fear of pulmonary toxicity. Several chemotherapeutic agents, including novel compounds such as irinotecan, gemcitabine, paclitaxel, and docetaxel, can cause severe pulmonary reactions that develop during, or shortly after, treatment.

Local administration of high doses of chemotherapy via inhalation may increase the risk of drug-induced lung disease. Furthermore, a high proportion of patients with lung cancer have impaired pulmonary function due to tobacco-related illness that could worsen the prognosis in the case of chemotherapy-induced lung disease.

So, we’ve got a built-in limitation here…

The risk of direct toxicity to the lungs must, therefore, be evaluated for each new drug considered for aerosol administration. Another safety issue is occupational exposure of healthcare workers to the nebulized drug. A recent study demonstrated the effectiveness of a mobile HEPA filter air cleaning system to prevent spread of aerosol during inhalation of nebulized cisplatin. I’m certain we would want to, at least, use a breath actuated nebulizer with a HEPA exhalation filter.

I don’t want any cisplatin unless I need it, let me make that quite clear.

Just to show you that there are people out there working on this, here’s a press release from 2002:

"Battelle Pulmonary Therapeutics, Inc. (BPT) recently received notice from the Food and Drug Administration (FDA) that its doxorubicin [Adriamycin] inhalation therapy has been designated as a fast track product for pulmonary broncho-alveolar carcinoma (BAC).

BAC is a type of non-small cell lung cancer with many unique biological and clinical characteristics. Unlike other types of lung cancer, BAC tends to spread within the lungs. If not treated in the early stages BAC is invariably fatal to patients, who die with severe pulmonary insufficiency and distress. BPT’s doxorubicin inhalation product combines a unique formulation and highly efficient patented delivery system, designed to provide treatment directly to the site of the tumor. This is the lead product in BPT’s growing inhaled therapy oncology franchise built around a proprietary technology platform for the treatment and prevention of respiratory tract cancers.

"BPT’s new inhaled chemotherapy is expected to provide benefit to these severely ill patients without adding serious systemic toxicities," said Tony Imondi, BPT’s Vice President of Regulatory and Clinical Affairs. Patients in Phase I trials who are taking doxorubicin [Adriamycin] by inhalation have tolerated the therapy with only minor side effects. "We are
extremely hopeful that we will be able to achieve levels of the drug in the lungs far exceeding that obtainable by IV delivery," Imondi said."

Of course, as in all press releases, this company is bragging. But it shows that there has been significant interest in this approach to treatment of lung cancer.

In order to be effective, aerosolized chemotherapy must be delivered at a sufficient concentration to the target area. Aerosol particle size is one of the most important determinants of aerosol dose and distribution in the lungs. We know this.

Aerosols with a mass median aerodynamic diameter (MMAD) of 5–10 microns are mainly deposited in the oropharynx and large conducting airways. Particles of 1–5 micron diameter are deposited in the small airways and alveoli with 50% of 3 micron diameter particles being deposited in the alveolar region. The typical nebulizer we use for treatments doesn't really do a good job of giving a uniform particle size, but it doesn't really need to. However, as we begin to think of more sophisticated uses for aerosol therapy, our nebulizers will need to follow suit.

The optimal site of deposition for aerosolized chemotherapy may be different for primary lung cancer located in or near the central airways, for broncho-alveolar carcinoma located in the alveolar region and for multiple parenchymal metastases.

Aerosol deposition in the target area can also be altered in the case of airway obstruction by the tumor or associated obstructive lung disease. The inhaled drug may reach the tumor either via direct topical penetration for bronchogenic carcinomas located close to the airways or via the local blood supply (bronchial or pulmonary circulation) for smaller primary or metastatic lung tumors located away from the airways.

Finally, little is known about the pulmonary metabolism of inhaled drugs, which may influence the therapeutic efficacy and pharmacokinetics of an aerosolized chemotherapeutic agent. There's always something.

Proof of Concept Studies

Pharmacokinetic advantage of inhaled chemotherapy:

Isotopic studies have been performed to compare pulmonary deposition of Adriamycin [the same stuff mentioned in the press release] in dogs after aerosol and IV administration at the same dosage. Compared with the IV route, aerosol administration of radioactively labeled Adriamycin
was associated with a marked increase in the level of radioactivity in the lungs with very low systemic concentrations of the drug after inhalation.

Note: Adriamycin is one of the most important chemotherapy agents used. It has been researched so heavily that 2,500 similar compounds have been created. Doxorubicin is commonly used to treat some leukemias, Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, multiple myeloma, and others. It has also been involved in HIV research.

Suffice it to say, we are not talking about a small time player here. As far as side effects are concerned….well let's just mention that it's nickname is "red devil". So, if we can treat the lung with low systemic levels, that's a very, very good thing.

An artist drew a painting about Adriamycin, which his mother had taken. This is that painting and his caption for it.

"That Red Fluid" (The Adriamycin Room) Amitai Ben David, 2000

"That red fluid" was the way my mother named the chemical-therapy medicine that was used on her in an attempt to fight her cancer. I accompanied her once to the hospital to see the dripping of this bright red medicine (Adriamycin) into her vein. My mother feared this medicine. Its weekly injection caused her, among other things, hair loss, and constant nausea. Eventually, her death was due to the devastating effect of the medicine, rather than the cancer cells themselves.

Sometimes, during the work on this painting, I felt as if I was painting a coffin. From the inside. The blue sky's reflection promised hope.
Koshkina et al. compared the pulmonary pharmacokinetics of a liposomal formulation of paclitaxel after aerosol and IV administration at comparative doses in mice. The deposition and clearance of the drug in the lung tissue extracts were determined using high-performance liquid chromatography. The authors found higher concentrations and slower clearance of paclitaxel from the lungs after aerosol delivery. The concentration in the lungs was 26-fold higher after aerosol delivery than after IV injection.

Good.

**Safety and anti-tumor effect of aerosolized chemotherapy:**

The cytotoxic effect of chemotherapeutic agents after nebulization has been studied in vitro using growth inhibition assays. Wang et al. assessed the cytotoxic properties of farnesol nebulized by two different nebulizers [Pari LC Star and LC Plus (vented, valved jet nebulizers) driven by a compressor, in two non small cell lung cancer cell lines. This study demonstrated that cytotoxic properties in vitro of farnesol are not altered by nebulization. So, that's good.

Gemcitabine [GCB] is a chemotherapeutic agent belonging to the nucleoside analog family. It has been demonstrated to be effective in the treatment of non small cell lung cancer, both as mono-therapy and in combination with other drugs. It is a pro-drug, which is inactive in the extracellular compartment. It becomes cytotoxic once it enters into a nucleated cell, in which it undergoes several phosphorylations. The GCB formulation does not contain any chemical compound incompatible with aerosol delivery.

Note: Gemcitabine is used in various carcinomas: non-small cell lung cancer, pancreatic cancer, bladder cancer and breast cancer. It is being investigated for use in esophageal cancer, and is used experimentally in lymphomas and various other tumor types. Gemcitabine represents an advance in pancreatic cancer care. It is also not as debilitating as other forms of chemotherapy.

Once again, a major player.

These advantages, combined with solubility in saline and the absence of irritant effects, make GCB an attractive candidate for local administration.

Similar cytotoxic properties have been observed with nebulized and non-nebulized GCB against similar non small cell lung cancer. The concentration of nebulized GCB causing 50% growth inhibition was similar to that previously observed with non-nebulized GCB.

Again, that's a good sign.

Several proof of concept studies of aerosolized chemotherapy have been performed in animal models of metastatic lung cancer. In these studies, animals were exposed to the aerosol generated by a jet nebulizer in a sealed plastic box. The amount of drug deposited in the lungs was estimated by taking into account the concentration of drug in aerosol volume, the volume of air
inspired by the animal in 1 min, the estimated deposition index, and the duration of treatment. [30 to 120 min.]

Using this procedure, the efficacy of aerosolized chemotherapy with liposome-encapsulated 9-nitrocamptothecin [Whew! Let's just call it L-9NC, ok?] was evaluated in two different experimental lung metastasis models.

In mice, L-9NC aerosols were started the day after IV injection of melanoma cells and were delivered for 1 hour, 5 days a week for up to 3 weeks. A preventive effect of aerosolized L-9NC was observed with fewer lung metastases in treated mice than in control mice.

Good.

In a second model, aerosols were started on the ninth week after osteosarcoma cells IV injection in nude mice. A curative effect of aerosolized L-9NC was observed against established lung metastases.

The murine RENCA model, based on IV injection of renal carcinoma cells, offers the potential advantage of a lack of early disease symptoms leading to the formation of distant metastasis, including the lungs. The anti-tumor effect of a liposomal formulation of paclitaxel delivered to the lungs by aerosol was studied in the RENCA model. Aerosols were initiated the day after renal carcinoma cell inoculation and were delivered for 2 weeks. A control group of mice received aerosols of blank liposomes. The study demonstrated a preventive effect of liposomal paclitaxel aerosols delivered 3 days per week with a reduced number of visible lung metastases and prolonged survival compared to control groups.

Living longer….fewer metastases….good.

A recent study from the same group evaluated the anti-tumor effect of aerosolized GCB compared to aerosolized saline in two models of osteosarcoma lung metastasis [nasty stuff]. Treatments were initiated 4 weeks after tumor cell inoculation when the presence of lung metastasis had been established. In this osteosarcoma lung metastasis model, the best therapeutic response was observed in mice treated with 1 mg/kg of GCB aerosol twice a week. No visible lung metastasis was observed 10.5 weeks after IV injection of human osteosarcoma cells.

After IV injection, these osteosarcoma cells grow subcutaneously then spontaneously metastasize to the lungs. In this model, GCB aerosol at a dose of 0.5 mg/kg three times weekly was compared to the same regimen via the IV route. Inhibition of lung metastasis was observed only in the GCB aerosol group compared to aerosolized saline. GCB administered by IV
injection had no impact on the number of lung metastases. Interestingly, a systemic effect of aerosolized GCB was observed with an inhibitory effect on subcutaneous tumor growth similar to that observed in the animals treated with IV GCB.

Good. We're getting some nice science to back up this idea.

The anti-tumor effect of aerosolized GCB has also been studied in an orthotopic model of large cell undifferentiated primary lung cancer based on intra-bronchial implantation of NCI-H460 cancer cells in BALB/c nude mice.(29) The histologic characteristics of orthotopic tumor models have been demonstrated to be consistent with the clinical tumor from which the cell lines are derived.

Furthermore, when cells are implanted intra-bronchially, tumors predominantly grow in the lung parenchyma. Weekly GCB aerosols were initiated the day after cell implantation for up to 9 weeks, using an endotracheal sprayer with scintigraphic assessment of pulmonary deposition as a model of aerosol delivery in rodents. Compared to control mice treated with aerosolized saline, weekly GCB aerosols were associated with complete inhibition of tumor growth in 31% cases and partial inhibition of tumor growth in the remaining cases. A dose effect of aerosolized GCB on tumor growth was observed. At the dosage of 8 mg/kg/week, aerosolized GCB was well tolerated, with no clinical and histologic signs of toxicity.

In a previous study Hershey et al. treated 24 anesthetized dogs with advanced stages of spontaneous primary lung cancer or lung metastases with paclitaxel or doxorubicin aerosols administered twice weekly. Tumor regression was achieved in 25% of dogs with measurable tumors without the systemic side effects normally associated with IV administration of these drugs and without pulmonary toxicity in the dogs treated with paclitaxel. Changes consistent with pneumonitis/fibrosis were observed in some dogs treated with doxorubicin aerosols.

Clinical Studies

OK, now we're getting big time.

One of the first reports of aerosolized chemotherapy in lung cancer was published by Tatsamura et al. in 1993. In this pilot study, 5-fluorouracil (5-FU) (250 mg in 5 ml) was delivered via inhalation using an ultrasonic nebulizer in patients with NSCLC in two situations.

In the first part of the study, pulmonary deposition of aerosolized 5-FU was documented in 19 patients with resectable NSCLC who received one aerosol 2 h before thoracic surgery. The authors demonstrated that aerosolized 5-FU accumulated at therapeutic concentrations in the trachea, bronchi, and regional lymph nodes along with 5-FU metabolites, FUR and FUdR, indicating that the drug was directly incorporated and metabolized in the respiratory tract. Only a
trace of 5-FU was found in the serum. Interestingly, 5-FU concentrations were 5- to 15-fold higher in the tumor than in normal lung tissue.

I like that one, too.

In the second part of the study, 10 selected patients with unresectable NSCLC were treated by daily 5-FU aerosols two to three times a week. None of the included patients had been previously treated. Six objective responses were observed, including four partial responses and two complete responses without stomatitis or any other significant pulmonary or systemic side effects.

Three phase I studies of aerosolized chemotherapy including dose escalation and pharmacokinetics have been performed in patients with primary or metastatic lung cancer who did not respond to previous conventional treatment. On the basis of previous successful trials, evaluation of aerosolized L-9NC was performed in 25 patients, including 6 patients with primary lung cancer. Aerosols were delivered 5 days/week via a mouth breathing-only face mask using a jet nebulizer in a HEPA-filtered airborne scavenging tent.

Interestingly, patients were allowed to self-administer treatment at home with a portable air compressor and a HEPA-filtering system if no side effect greater than grade 2 was observed. The dose-limiting toxicity (DLT) of aerosolized L-9NC was chemical pharyngitis. Grade 2 toxicity included: nausea/vomiting, cough and bronchial irritation and fatigue. A reversible 20% decrease of FEV1 was observed. [sounds like a little bronchospasm]

There was no hematological toxicity. Very cool. In five patients, bronchoscopy with broncho-alveolar lavage (BAL) at the end of treatment revealed L-9NC concentrations 4 to 10 fold higher in BAL fluid than in plasma. Partial remissions were observed in two patients with uterine cancer, and stabilization occurred in three patients with primary lung cancer. A partial remission of a liver metastasis was also observed, confirming the systemic potential of aerosolized L-9NC previously observed in animal models.

This study was the basis for the recommended dosage for two ongoing phase II trials of aerosolized L-9NC: one in primary lung cancer, and one in metastatic endometrial cancer (ClinicalTrials.gov). Two phase I studies were published in 2007.

There's more science to lean on here than there is with some of the other things we do, like, say, EzPAP or CPT, for example.

Finally, the safety and pharmacokinetics of aerosolized cisplatin encapsulated in lipid vesicles was recently investigated in 17 patients with histologically proven lung cancer - NSCLC. Aerosols were delivered 1 to 4 consecutive days in 21-day treatment cycles. The number of daily inhalation sessions in combination with the number of treatment days was considered to be the limiting factor and no dose limiting threshold was achieved at the maximum delivered dose. …meaning that the nasty cisplatin did not cause pulmonary airway effects bad enough to cause symptoms in the patients.
Apart from nausea and vomiting, the most commonly observed adverse events concerned the respiratory tract (including a grade 1–2 decrease in FEV1 and DLCO), but the usual systemic toxicity of cisplatin (hematologic toxicity, nephrotoxicity, ototoxicity) was not observed.

Very good. This makes me want to send a little aerosol right on top of this bad boy:

![Image of lungs with lesions]

Some aerosol full of Adriamycin or cisplatin.....something that he really wouldn't like.

Pharmacokinetic data showed very low plasma platinum levels. Best overall response observed in this study was stable disease in 12 patients. On the basis of successful preclinical experiments on weekly aerosol delivery of GCB in animal models, a phase I study is ongoing in patients with NSCLC. Weekly GCB aerosols are delivered via a chamber (Idehaler™, Atomisor, France) operated with a mesh nebulizer (Aeroneb™, Pro, Aerogen, Mountain View, CA) (MMAD 5 microns) in a specially designed closed cabin equipped with an air extraction and filtering system. Assessment of the delivered dose is performed at the first inhalation using a tracer. Preliminary results in six patients demonstrate the feasibility of 9 weekly aerosols of 0.5 and 1 mg/kg of GCB.

It worked.

When you saw the phrase ‘closed cabin’, what did you see in your mind?

Something like this?

![Image of a closed cabin]

Me too.
But, what they probably did was modify one of these old friends of ours:

![Image of medical equipment]

Maybe we'll end up grabbing one of these from the back of the equipment room and dusting it off. One thing will be different, though. This time it will do some good.

**Conclusions and Perspectives**

Preclinical studies in animal models have demonstrated the safety, pharmacokinetic advantage, and anti-tumor effect of aerosol administration of several chemotherapeutic agents including doxorubicin, gemcitabine, and liposome-encapsulated formulations of paclitaxel and 9-NC.

Recent phase I studies demonstrated the feasibility of aerosol delivery of doxorubicin and liposomal formulations of 9-NC and cisplatin in patients with primary and metastatic lung cancer with a limited pharmacokinetic profile consistent with the observed low systemic toxicity.

Most adverse events of aerosolized chemotherapy were due to direct effects of the inhaled drug on the upper and lower respiratory tract, including pulmonary dose-limiting toxicity for Adriamycin. Although the advanced stage of the disease in patients included in phase I studies makes it difficult to draw any conclusions regarding the efficacy of aerosolized chemotherapy, some responses were observed including partial remission of liver metastasis in the L-9NC study demonstrating a potential systemic effect of the inhaled drug.

Further studies integrating safety, pharmacokinetic, and efficacy considerations are required to determine whether there is room for local administration of chemotherapy via inhalation in lung cancer. For each new drug considered for aerosol delivery, pre-clinical studies including a
deposition study are required for safety assessment. We always have to do that, of course. We're never finished, really.

Sustained release from a therapeutic aerosol can prolong the residence of an inhaled drug in the airways or alveolar space increasing local efficacy and reducing dosing frequency.

Liposomes can be used to encapsulate a variety of drugs with a wide range of lipophilicities. The lipid nature of the sphere can promote phagocyte uptake and absorption into lymphatic vessels commonly involved in tumor metastasis. A study of 5-FU in lipid-coated nanoparticles administered by inhalation to hamsters demonstrated targeted drug-delivery and sustained effective 5-FU concentrations in the lungs. Good deal.

Several strategies could be considered for the use of aerosolized chemotherapy in thoracic oncology. In primary lung cancer, regional chemotherapy via inhalation could be useful in selected situations. Broncho-alveolar carcinoma, a rare form of NSCLC composed of alveolar epithelial tumor cells filling up the alveolar space and gradually inducing respiratory insufficiency or evolving into invasive adenocarcinoma, could constitute a potential indication for aerosolized chemotherapy.

Regional drug delivery via the airways could allow direct exposure of cancer cells to the therapeutic agent. Aerosolized chemotherapy could also be useful in unresectable main bronchus carcinoma with limited invasion or tumor relapse after surgery. Inhaled chemotherapy could be considered as adjuvant therapy in combination with other treatment modalities such as surgery or systemic chemotherapy in advanced disease.

Aerosol therapy could have potential applications for local administration of chemo-preventive agents. In a hamster model, aerosol delivery of 5-FU was demonstrated to reduce the occurrence of infiltrating squamous cell carcinoma of the upper respiratory tract induced by local instillation of methylnitrosourea. Several non-chemotherapeutic agents may also take advantage of local delivery through the respiratory tract, such as activators of the local immune system, gene therapy, and COX-2 inhibitors.

Looks like I'll have to cut this short, so you can do whatever you plan to do next.

And I haven't even told you about some exciting studies done with children at M.D. Anderson Cancer & Tumor Institute in Houston. Children really like this idea. Know why?

Yep. No needles.

Use of the aerosol route to deliver medication is finally gaining the attention it should, it seems.
Treatment of Dyspnea and Pain with Nebulized Morphine

As we as therapists know all too well, shortness of breath is commonly seen in patients with a wide variety of conditions. We constantly see our patients suffer. We see them in terminal conditions such as cancer. We see them suffering during exacerbations of COPD, pulmonary fibrosis, and CHF, among other nasty things.

Between one third and one half of the general cancer population experience dyspnea and the incidence increases up to 70% for those in the terminal stage. Realize, we're talking all types of cancer here. In over 20% of these patients, dyspnea is reported to be the primary symptom.

In contrast to pain, which tends to be well-controlled in the final weeks of life, dyspnea progressively increases in frequency and intensity, particularly in those with primary lung cancer. As we know, shortness of breath disturbance evokes the most intense sense of impending doom. I've seen patients experiencing the angina of an impending MI look relaxed compared with my dyspneic patients. And in those suffering from terminal illness, dyspnea provokes psychological suffering, as it is invariably associated with impending death.

In these situations, we usually cannot reverse the underlying cause of dyspnea, so easing of the symptom becomes the primary goal. Opiates have been used to treat dyspnea since the late 19th century, but their use fell from favor in the 1950's, once a clear relationship with respiratory depression was established. We soon learned that opiate receptors were present throughout the body: this raised in many clinicians' minds the possibility that a direct pulmonary-targeted treatment for dyspnea with aerosolized opiates might be possible with less adverse effect. We've all certainly seen the adverse effects of systemic administration of morphine and fentanyl.

Dyspnea: Feelings of Air Hunger

The perception of difficulty breathing is a rather complex thing, actually. Realize that we are talking about a subjective thing here. Dyspnea is the perception of difficulty with breathing. As with all perception, dyspnea is interpreted within the context of previous experience and
learning, so that an individual’s reaction to dyspnea frequently changes over time. Therefore, the intensity of distress that accompanies dyspnea is highly individualized, and objective measurements often bear little resemblance to how patients are feeling. We've all seen the patient with a reasonable respiratory rate and minor chest retractions feeling as though they won't last another ten minutes…and patients who clinical signs of extremely high work of breathing who seem mildly distressed by the situation.

One way I like to put it is that dyspnea is an imbalance between the perceived need to breathe and the perceived ability to breathe.

It is important to emphasize that efferent discharge from the respiratory centers in the brain stem represents a complex processing and integration of multiple inputs, which include: afferent information regarding peripheral chemoreceptor stimulation; force-displacement in the chest wall; lung stretch; central chemoreceptor stimulation; and information from higher levels in the brain.

A useful concept for understanding dyspnea is length-tension inappropriateness. When signals to the respiratory muscles cause contraction, mechanoreceptors in muscle fibers, tendons and joints, and also in the airways and alveoli, send information that conveys both the velocity and degree of displacement occurring in the chest wall and lungs.

In this way, effort [think of this the strength of the signals from the respiratory centers in the brain stem], force developed in the inspiratory muscles, and displacement of the lungs and chest wall are compared. Through habituation we come to experience a specific relationship between these elements as “normal breathing.” Minor breath-to-breath imbalances that develop between force and displacement are processed in order to adjust breathing effort and maintain minute ventilation.

However, when tension in the ventilatory muscles is excessive, relative to both the shortening of the muscle fibers and the stretch of the lung tissue, dyspnea is felt, as heightened signals to the respiratory muscles also cause conscious awareness of breathing. Likewise, dyspnea can occur in the presence of muscle weakness or fatigue, when length-tension appropriateness may be preserved but effort is disproportional to chest displacement. Of particular interest is the fact that dyspnea can be evoked by elevated carbon dioxide alone.

Furthermore, the situation in which these signals occur impacts the interpretation of breathing sensations. For example, during heavy exercise, the corresponding respiratory effort and work load are elevated, but this does not provoke distress because it is appropriate to the circumstances, and respiratory effort can be reduced simply by decreasing the activity level. However, if the same breathing pattern were to occur when sitting quietly in bed, it would cause alarm, as the breathing pattern is inappropriate. More importantly, this implies that the individual cannot do anything to resolve the situation.
Dyspnea in Terminal Illness

When it's possible, of course, we should treat the cause of the dyspnea, rather than try to simply treat the symptom. Because multiple physiologic inputs are responsible for generating dyspnea, numerous pathophysiologic disturbances can impact the intensity and quality of the sensation. When examining factors that contribute to dyspnea in advanced diseases, it is apparent that some factors can be treated readily, whereas others are not amenable to rapid reversal. Thus, treatment should focus initially on salient causes of dyspnea, such as correction of hypoxemia with supplemental oxygen, acute hypercapnia with noninvasive positive-pressure ventilation, reversal of bronchospasm with beta agonists and steroids, relief of chest wall restriction by drainage of pleural effusions or ascites, and reduction of pulmonary edema with diuretics. Palliative therapy with aerosolized opiates should be considered only when conventional approaches do not produce satisfactory results or corrective treatment is not plausible. In particular, muscle weakness, anxiety, and panic appear to be common features of advanced disease that greatly impact dyspnea but may not be amenable to standard therapies, and thus may form a strong rationale for using aerosolized opiates.

Pharmacology

In the 1970s it was found that the central nervous system produces endogenous opiates (endorphins) that are important in regulating not only the perception of pain, but also sleep, learning, memory, and appetite. In particular, endorphins are produced in response to both stress and chronic pain. Endorphins inhibit impulses, so that the perception of pain is either altered or inhibited. The medulla was discovered to be rich in opiate receptors which helped us understand the effects of opiates on respiratory drive.

Although they do not play a regulatory role in the control of breathing in normal subjects, endorphins blunt the ability of patients with COPD to compensate for increased work of breathing. This is separate from carbon dioxide sensitivity. That's another subject for another
day. Similar to the body’s response to chronic pain, the brain produces endorphins as an adaptive response to the chronic stress associated with increased work of breathing.

A similar effect is achieved with oral codeine, which improves mobility and dyspnea in ambulatory patients with COPD, and with subcutaneous morphine sulfate to ease dyspnea in patients with terminal cancer.

It has been found that the lungs also may contain a novel opiate receptor. Animal studies have revealed the presence of opiate receptors in the trachea, bronchi, and pulmonary arteries, but these receptors are particularly prominent in the bronchioles and the alveolar walls near the pulmonary capillaries.

There are different types of opiate receptors in the pulmonary system. Pulmonary opiate receptors are associated primarily with vagal afferent C-fibers (irritant or rapidly-adapting fibers) and the juxta-pulmonary capillary receptors (J-receptors), which are located in the alveolar wall. Stimulation of C-fibers in the small airways and J-receptors in the alveoli by acute pulmonary congestion and edema, multiple pulmonary embolism, and inflammation may be responsible, in part, for triggering the sensation of dyspnea, as well as tachypnea, bronchoconstriction, and increased airway secretions.

In a manner similar to that seen with pain, opiates may alter the perception of dyspnea by modifying signals from pulmonary C-fibers. A third type of vagal fiber is the pulmonary stretch receptor which, when stimulated, typically by large tidal volumes, reduces the sensation of air hunger. Inhaled opiates also may act on these fibers.

Pharmacokinetics

Despite the anatomic evidence cited above, it remains unclear whether the effects of aerosolized opiates on dyspnea are due to modifications in peripheral afferent signaling that alters proprioception, or that opiates absorbed into the systemic circulation act on central nervous system control of breathing. Most studies that have examined inhaled opiates did not observe signs of sedation or respiratory depression. However, hypercapnia and profound respiratory depression occasionally have been reported. Inhaled opiates also provide effective analgesia which suggests the possibility that dyspnea is modified, at least in part, through a central mechanism. Systemic absorption of opiates may occur from the pulmonary circulation. But a more likely source is absorption from the gastrointestinal tract, due to aerosol impaction in the oropharynx and subsequent swallowing of opiate-containing secretions. Yet in cancer patients who suffer from intractable dyspnea, relatively small amounts of inhaled opiates appear to improve breathing comfort, despite the fact that these patients already are receiving high levels of parenteral opiates for pain management.

Six studies have assessed absorption and bioavailability of morphine, morphine-6-glucuronide (a potent metabolite of morphine), and fentanyl, administered via jet nebulizer with mask, during spontaneous breathing, via endotracheal tube during passive mechanical ventilation, or with a
prototype breath-actuated unit-dose nebulizer during spontaneous breathing.

Sounds like plenty of folks are interested in this.

All of these studies were carried out on healthy volunteers with normal pulmonary function. In the most widely cited study, Chrubasik et al reported that serum morphine levels following inhalation varied widely among individuals, with a relative systemic bioavailability of 17% (range 9–35%). The maximum serum morphine concentration was achieved by 45 min and was approximately 6 times lower than with intramuscular administration.

Masood and Thomas reported that, although peak plasma concentration was achieved within 10 min with aerosolized morphine, systemic bioavailability was only 5%, compared to 24% with oral administration.

In contrast, Ward et al reported similar time course and bioavailability profiles for the inhaled and intravenous administration routes. This may be explained by the use of a highly efficient, non-conventional nebulizer, and measurement of arterial plasma rather than venous plasma concentration.

So, there's learning to do with this stuff. I'm glad we've got some people working on it.

These pharmacokinetics studies suggest that systemic absorption and a central action of aerosolized opiates cannot fully explain the apparent effects on dyspnea, particularly in patients already receiving systemic opiates for analgesia.

That's means something good is happening IN the lungs, friends. Right where we want it to happen.

The wide range in systemic bioavailability found in mechanically ventilated subjects with normal lungs may reflect variability in jet nebulizer performance, coupled with the limitations of drug delivery imposed by the artificial airway and a passive breathing pattern. These studies also have limited relevance to patients with advanced pulmonary disease, because pathologic alterations in airway geometry and pulmonary perfusion, along with abnormal breathing patterns, would probably alter drug deposition.

**Management of Dyspnea**

Interestingly enough, there are more than 30 studies that have been done involving nebulization of opiates.

Seven of these were small prospective randomized placebo-controlled trials that examined the effects nebulized morphine on exercise endurance in patients with stable COPD or pulmonary
fibrosis, or in healthy volunteers. There also have been 13 (mostly uncontrolled) studies and case reports on the effects of aerosolized opiates in end-stage cardiopulmonary disease (COPD, pulmonary fibrosis, and congestive heart failure), advanced cancer, and cystic fibrosis. In one unusual case report, a patient with severely debilitating paroxysmal coughing was successfully treated with aerosolized morphine. That tells us something right there.

Five of the 6 double-blinded randomized placebo-controlled studies that examined the effects of aerosolized opiates in patients with COPD or pulmonary fibrosis reported no improvement either in exercise tolerance or dyspnea, compared to placebo. In the one positive study, the improvement in exercise endurance was minor. So, it looks like this won’t be the way to help these folks.

But, here comes the magic…..

On the other side of the coin, all of the uncontrolled trials that examined the effects of aerosolized opiates in patients with end-stage disease (usually metastatic cancer) reported subjective improvements in dyspnea, paroxysmal coughing, and breathing pattern following aerosolized opiates.

That’s good to hear, indeed.

Characteristically, in these studies patients appeared to have intractable dyspnea despite receiving generous amounts of intravenous or oral opiates for pain management. Yet supplementation with 5 to 10 mg of aerosolized morphine sulfate, repeated either as-necessary or every 4 h, almost uniformly improved dyspnea, breathing pattern, and the general appearance of these patients. In patients with opiate tolerance the dose often needed to be increased to approximately 20 mg, and in the final days of life, doses as high as 45–70 mg sometimes were required.

As morphine sulfate can cause bronchospasm from histamine release, some have added a 2–4-
mg dose of dexamethasone [Decadron] as prophylaxis. Others have used an initial test dose of only 2.5 mg morphine sulfate to evaluate any tendency for bronchospasm prior to administering a higher dose. Fentanyl does not cause histamine release and therefore is an attractive alternative in severely dyspneic patients with reactive airways disease. Doses of 20 –100 mg of fentanyl have been used to treat dyspnea. With hydromorphone [Dilaudid], an initial aerosolized dose of 1–2 mg every 4 hours has been recommended, but doses as high as 4–8 mg every 4 hours have been used.

Only 2 prospective, randomized, double-blinded, placebo-controlled trials have examined the efficacy of aerosolized opiates on dyspnea in patients with advanced disease. Noseda et al found no benefit from 10 mg or 20 mg of aerosolized morphine citrate on dyspnea in 17 patients with severe chronic lung disease or metastatic cancer.

In contrast, Bruera et al found that aerosolized morphine sulfate given to patients with metastatic cancer was as effective as subcutaneous administration in reducing dyspnea. These discrepant results may be explained by the fact that 12 of the 17 patients in the study by Noseda et al had COPD, whereas only 3 had metastatic cancer. Two of the patients with cancer died before completing the protocol, and their data were not included in the analysis.

In addition, Noseda et al measured dyspnea only 10 min after completion of nebulization, which based on the results of aerosolized opiate studies for pain management, may have been an insufficient amount of time to accurately judge efficacy.

Which goes to show you; just because it's a study, that doesn't mean it was done right.

Let me close this little section with a quote from an esteemed palliative care physician, Dr. James L. Hallenbeck. His comments regarding nebulized morphine are fairly typical of those smart physicians who have experience in the treatment of end of life issues:

"Opioids are very effective in relieving dyspnea, although the exact mechanism is not understood. Contrary to common belief, this effect does not result through inhibition of respiratory drive. Relief from the "work of breathing" is a function of steady-state opioid levels, much like steady-state opioid levels relieve pain.

Inhibition of respiratory drive results primarily from rising opioid serum levels. Studies have demonstrated significant relief of dyspnea from opioids without significant effects on ventilation or pCO₂ levels in common therapeutic doses. Having said this, patients with dyspnea are fragile. Respiratory drive suppression can occur if serum opioid levels rise rapidly. Thus, when initiating therapy with opioids for dyspnea, one should start with a low dose and raise the dose slowly as needed."
Morphine is the best studied of the opioids for relief of dyspnea, although relief has been observed with other agents, such as oxycodone, fentanyl, and methadone. There is no demonstrated advantage of one opioid over another. Generally, a lower dose of opioid is required to relieve dyspnea than is needed to relieve pain.

Nebulized morphine has been used by some to treat dyspnea, although this is not an FDA-approved route of administration in the United States. Specialized morphine have been identified in the lung, and it has been theorized that binding of these peripheral receptors may relieve dyspnea at lower serum levels of morphine than when it is given via other routes. Studies have demonstrated that aerosolized morphine is effective in the relief of dyspnea, although no clear advantage of this route has yet been proven other than its rapid onset of action. Few bioavailability studies have been done. From 5% to 100% bioavailability has been reported. I believe it safest to assume 100% bioavailability, at least with initial dosing.

One advantage of the aerosolized route is that peak serum levels occur rapidly - roughly equal to the time it takes to deliver the aerosol. This can be an advantage over oral dosing (peak effect in one hour) and parenteral administration, which may not be feasible in certain settings, such as in the home.

Morphine can cause histamine release, thereby inducing bronchospasm when given by aerosol. It may be wise to give a trial dose under observation and to watch for bronchospasm. It seems advisable to ensure that patients are able to tolerate non-aerosolized morphine with no histamine release before attempting aerosol therapy.

There has been some concern that the preservatives for regular IV morphine may trigger bronchospasm, although, to my knowledge, this is only theoretical. Thus, some authors have recommended using preservative-free morphine when using aerosol. I have successfully used injectable morphine in a number of patients with no evidence of adverse effect.

In my practice I have used this route primarily when a patient is already receiving other nebulized medications to which morphine can be added or when rapid, non-parenteral (IV, SC) dosing is desired. Responses appear to be somewhat idiosyncratic. Some patients love it, while others are unimpressed. I recommend starting with a low dose, 2-4 mgs. I have not read of experiences with other opioids administered via this route.”

So, this physician, who has dealt with dyspnea management, certainly sees a niche for aerosolized morphine. In fact, it looks like he was interested enough to have read the studies. Impressive.

Here’s a picture of Dr. Hallenbeck early in his residency:

The obviously kind-hearted Dr. Hallenbeck
Here's a photo of him a few years later:

After some wisdom and weariness had set in. Treating dyspnea is no ride in the park, folks. I believe he was 32 at this point.

**Aerosolized Opiates in the Management of Pain**

Seven studies have evaluated aerosolized opiates for analgesia in postoperative management following general surgery, chest trauma, sickle cell crisis, and management of pain in the emergency department setting. All the studies found that aerosolized opiates provide adequate analgesia, and several reported a lower incidence of adverse effects, including sedation.

Not too shabby, that.

Average doses that provide adequate analgesia appear to be 12–20 mg morphine sulfate every 4–6 hours, and 150–300 mg fentanyl citrate. Only one of the studies with fentanyl allowed repeated supplemental administration, which was at half the initial dose.

When compared to intravenous administration, aerosolized opiates tend to have a slower onset of action, but the quality of analgesia is not different by 30 minutes. Some studies reported onset of pain relief in 3–5 min. Although routinely administering aerosolized opiates for analgesia has been criticized as awkward and inefficient, it may be useful in patients in whom either intravenous access is difficult or the adverse effects of sedation must be avoided. And, those patients do exist.

**Occupational Risks**

Health care professionals have a propensity for developing chemical dependencies. Anesthesiologists appear to be at particular risk, and this has been attributed to a combination of high job stress and extraordinary access to controlled substances. Yet others postulate that
inadvertent aerosolization of intravenously administered opiates in the exhaled gas may sensitize health care workers through “second-hand” exposure. Over time this sensitization may enhance the probability of addiction.

Aerosolized fentanyl and propofol have been detected in the operating theater and in the expiratory limb of anesthesia ventilator circuits. This raises concern regarding occupational risk. However, the potential for aerosolized opiate exposure is much greater in the critical care environment, given the tremendous frequency of intravenous infusions of high-dose opiates and the elevated minute ventilation demands of patients.

Yet there is no evidence of widespread opiate addiction among critical care practitioners, which suggests that access to these drugs without stringent accountability is a more likely explanation. At this juncture, theoretical concerns over health care worker exposure should not preclude consideration of aerosolized opiate therapy in patients with terminal illness.

Or, how about this? Let's use high efficiency nebulizers with expiratory filters for this special task. We have those now. Life is good.

**Conclusion**

So, it looks like aerosolized opiates are not something that will help our patients with COPD or pulmonary fibrosis which is not complicated by other conditions.

**Clinical evidence supports aerosolized opiates for palliation of dyspnea in patients with advanced cancer and cystic fibrosis.** That's one of the most important sentences in this little discussion.

I had the privilege to work with a wonderful physician who specialized in pain management for a couple of years. That got me interested in this subject. I saw first hand the relief from dyspnea that my cancer patients felt after administration of nebulized morphine. And they were alert after the treatment........... Alert and able to breathe........... Wonderful..... I'll never forget it.

There is also some higher level clinical evidence that aerosolized opiates can be utilized for systemic pain relief. However, this should be restricted to circumstances where effective parenteral administration is delayed because of difficulty in achieving intravenous access.

*Have you ever had a patient in the ER in pain while the nurses were trying to get an IV started?*

*(see picture next page)*


*Let's assume this is a trauma patient screaming in pain. He's hypotensive from blood loss. Several of these folks have been trying to obtain IV access for 10 minutes. Wouldn't you like to be the one who asks for a quick verbal order for a little nebulized morphine? I would. Would you sleep well that night? Yes, you would.*

Well, I hope this has been helpful to you and proves to be something you can recommend in your own practice.

This is one of my favorite subjects. Great to know about. For those patients who need this, it can be very helpful. More helpful than EZPap, but then almost everything is.

In case your physicians are reluctant, here are some references……They ought to help.
References


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