Should Aerosolized Antibiotics Be Administered to Prevent or Treat Ventilator-Associated Pneumonia in Patients Who Do Not Have Cystic Fibrosis?

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Ventilator-associated pneumonia (VAP) significantly increases intensive care unit morbidity, mortality, and costs. VAP is thought to be caused by bacterial entry into injured airways, which produces tracheobronchitis that evolves into diffuse pneumonia. The use of aerosolized antibiotics is conceptually attractive, especially when the infection is early and limited to the airway epithelium. Data show that aerosolized antibiotics kill airway bacteria and improve outcomes in cystic fibrosis. The clinical evidence for aerosolized antibiotics to prevent VAP is weak but suggestive. Concerns about the high cost, possible development of antibiotic resistance, and other potential risks of aerosolized antibiotics led several evidence-based consensus groups to recommend against routine use of aerosolized antibiotics for VAP prevention until better data are available. Importantly, the clinical evidence that aerosolized antibiotics can treat established VAP is negative, and multiple consensus groups recommend against treating established VAP with aerosolized antibiotics. *Key words: pneumonia, ventilator, aerosol, antibiotics, ventilator-associated pneumonia, cystic fibrosis.*
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Introduction

Ventilator associated pneumonia (VAP) is an important complication of mechanical ventilation.[1–7] VAP is estimated to occur in up to 45% of patients who are ventilated for more than 5 days, and VAP significantly prolongs mechanical ventilation, increases exposure to ventilator-induced lung injury risks, and substantially increases costs.[2–5]

VAP is initiated by a breakdown in barrier defense and airway entry of potential pathogens.[7–23] First, the physical

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barriers (ie, glottic and laryngeal structures) that protect the airways from pharyngeal contents are compromised when an endotracheal tube is placed. Despite the balloon cuff that is usually present on these tubes, liquid aspiration around the cuff is common.[10–14,18] Second, supine patients with compromised esophageal and gastric motility routinely have stomach contents present in the pharynx, which contributes to aspiration.[19] Third, aspiration into injured airways with compromised host defenses is characteristic of systemic diseases and leads to infectious tracheobronchitis.[7–19] Finally, this infectious tracheobronchitis spreads into the alveolar regions, producing VAP. Aerosolized antibiotics have been proposed for (1) treating tracheobronchitis to prevent VAP, and (2) treating established VAP, perhaps in conjunction with systemic antibiotics.

Pro: Aerosolized Antibiotics Should Be Used to Prevent and Treat VAP

Reducing Airway Bacterial Load Reduces VAP Development

Numerous data support the concept that reducing the bacterial load in the tracheobronchial tree prevents VAP.[24–26] A carefully performed study with baboons showed that aerosolized antibiotics prevented pneumonia associated with acute respiratory failure.[24] More importantly, 2 evidence-based reviews[25,26] strongly supported semi-recumbent positioning, maintenance of ventilator circuit integrity, subglottic suctioning, and other measures such as specialty beds to mobilize secretions, as effective ways to reduce VAP. Common among all these approaches is the idea that reducing bacterial entry into the tracheobronchial tree will reduce VAP. Although neither of these reviews found good randomized trials that used aerosolized antibiotics and recommended their use (see below), the other available data support the concept that eliminating bacteria in the tracheobronchial tree can prevent VAP.

Aerosolized Antibiotics Kill Bacteria in the Tracheobronchial Tree

Aerosolized antibiotics can produce very high sputum-to-serum ratios.[27–29] Moreover, a large body of literature shows that aerosolized antibiotics kill large numbers of bacteria in tracheobronchial secretions.[27] Much of this literature comes from the cystic fibrosis (CF) population, but it is reasonable to extrapolate these data to the concept that aerosolized antibiotics would kill organisms associated with the tracheobronchitis of mechanical ventilation, many of which are similar to the typical CF pathogens *Staphylococcus* and *Pseudomonas*. Indeed, one group found that topical antibiotics may reduce sputum volume and sputum bacterial growth in ventilated patients at risk for VAP.[30] Topical antibiotics are also used to treat skin infections, gastrointestinal infections, peritoneal infections, and cystitis, which further suggests that these could be effective in the airway.

Aerosolized and Other Topical Antibiotics Have Proven Benefit in Airway Infections

Aerosolized antibiotics kill infectious organisms very effectively in CF airway secretions and have been used for years to treat airway infections in CF patients.[31] In CF patients, aerosolized antibiotics improve pulmonary function (eg, forced expiratory volume in the first second) and reduce the need for hospitalization. Smaller studies found similar results in patients with bronchiectasis.[32–34]

In 2006, a Cochrane Database review[35] on topical antibiotics in the oropharynx of non-CF, mechanically ventilated patients found that reducing the bacterial load in the posterior pharynx with selective gastrointestinal-tract decontamination significantly reduced VAP. One can extrapolate these data to the concept that reducing bacterial load in the tracheobronchial tree would also significantly reduce the rate of VAP.

Clinical Trials to Date: The Positive Spin

A number of trials over the last 3 decades have supported the use of aerosolized antibiotics for preventing VAP.[36–42] An early randomized controlled trial by Klastersky et al[39] in 1974, and non-randomized trials by Klick et al[41] in 1975, and Vogel et al[42] in 1981, found less VAP with inhaled gentamicin or polymyxin. However, because those results were not duplicated in other randomized controlled trials,[38,40] and because of concern about antibiotic resistance,[43] there has not been widespread acceptance of inhaled antibiotics.

More recent studies by Rathgeber et al[37] and Wood et al[36] with aerosolized tobramycin and ceftazidime, respectively, found a reduced VAP rate without the development of antibiotic resistance. Although not a randomized trial, a large observational trial by Rouby et al[44] also suggested less VAP, without important antibiotic resistance issues, with aerosolized colistin.

In 2006, Falagas et al[45] performed a meta-analysis on the 5 available randomized controlled trials (Table 1), and they suggested significant benefit from aerosolized antibiotics, in that they prevented VAP, though mortality was not affected (Fig. 1).

Con: Aerosolized Antibiotics Should Not Be Used to Prevent or Treat VAP

Clinical Trials to Date: The Negative Spin

Antimicrobial effectiveness should be established by well-controlled randomized trials. Careful review of the

Table 1. Randomized Controlled Trials of Aerosolized Antibiotics to Prevent VAP

First Author, Year	*n*	Antibiotic	Outcomes
Wood[36] 2002	40	Ceftazidime	Less VAP, lower cytokines
Rathgeber[37] 1993	69	Tobramycin	More systemic antibiotics in controls
Lode[38] 1992	25	Gentamicin	No effect
Klastersky[39] 1974	85	Gentamicin	Less VAP
Greenfield[40] 1973	58	Polymixin	No effect

VAP = ventilator-associated pneumonia

literature shows that there are insufficient published data to clearly support inhaled antibiotics for treating established VAP. Specifically, the trials by Klastersky et al[46] and (more recently) Michalopoulos et al[47] both showed limited benefit from aerosolized antibiotics in treating established VAP in non-CF patients. Several evidence-based reviews have stated that aerosolized antibiotics will probably never be proven effective, either as monotherapy or more effective than systemic therapy in treating established VAP.[48–50]

The data on aerosolized antibiotics to prevent VAP are less clear. It is important to note that of the 5 peer reviewed trials listed in Table 1, the largest trial did not reach statistical significance, another was clearly negative, and a third used only an indirect measurement of effectiveness (less systemic antibiotic use in the treated group). Probably the strongest data come from the small study by Wood and colleagues,[36] who found reduced VAP with aerosolized ceftazidime, but, strangely, found no effect on bacteriology results. Moreover, the use of ceftazidime as the aerosol agent in that trial poses some problems, as discussed below.

Several recent evidence-based reviews have interpreted these supporting data as weak, and, when considered in the context of the potential problems discussed below, have universally recommended against routinely using aerosolized antibiotics for VAP prophylaxis until stronger supporting data are available. As an example, one review concluded that "despite optimized delivery systems. . . inhaled antibiotics can still not be recommended for preventing VAP. . . in most patients."[49] Another review stated that "although the theory behind aerosolized antibiotics seems to be sound, there are limited data available to support the routine use of this modality."[50]

Problems With Aerosolized Antibiotics

There are a number of potential problems when using aerosolized antibiotics. First is the issue of antimicrobial penetration. Aerosolized antibiotics land on the surface of the sputum and can diffuse only so far. Established, deep-seated infections in which only the surface of the inflammatory process is accessible by the airways will probably be unresponsive to an antibiotic present only in the airway. This problem is compounded when using less efficient nebulization systems.[51] Because of these issues, inhaled antibiotics are not used to treat acute pneumonia in CF patients. Instead, systemic oral or intravenous antibiotics are nearly always used in combination and in high dose, to allow penetration into the deeply infected airway.[52]

The development of antibiotic resistance is another important concern. The bacteria just below the surface of the sputum-air interface might be the most likely group to develop resistance. Specifically, the bacteria on the surface will be killed, but the bacteria below the surface may have the opportunity to develop resistance.[53] Of perhaps greater importance and danger, bacteria in conducting airways that may be encased in biofilm will be exposed to an antibiotic concentration below the minimum inhibitory concentration and will not die, but this low concentration of antibiotic will promote the development of resistance and increase the difficulty of treating a resurgent infection by these organisms and the risk to other patients in the same intensive care unit (ICU).[53]

Antibiotic resistance development has occurred in virtually all of the CF studies that have evaluated aerosolized antibiotics.[31] Moreover, resistance issues were substantial in several of the early controlled trials of aerosolized antibiotics for VAP prevention[37,39,40] and in a large observational trial.[43]

Other problems related to nebulizing antibiotics include bronchospasm from the aerosol[54] and systemic toxicity, including renal failure from aerosol aminoglycosides, which can be absorbed across the inflamed airway.[55] Delivering aerosol antibiotics to a ventilated patient requires changing ventilator settings and gas flow,[56] and although this is manageable, it does require an astute awareness of the potential problem. There is also a small but significant risk of introducing infection with aerosol therapy if care is not taken to maintain sterility of the nebulization apparatus.[57]

Finally, aerosol antibiotics are expensive! Tobramycin solution for inhalation costs about $2,000 for a 28-day supply of the drug, when given daily for CF therapy. For preventing or treating VAP it is not clear what drug should be used, what dose should be used, when the medication should be started, the appropriate frequency of use, or the appropriate duration of use. Decisions that sound simple—such as starting an aerosolized antibiotic on all intubated patients upon admission to the ICU or waiting until they have been on a ventilator for 5 days or have developed some signs of tracheobronchitis—can profoundly impact hospital costs.

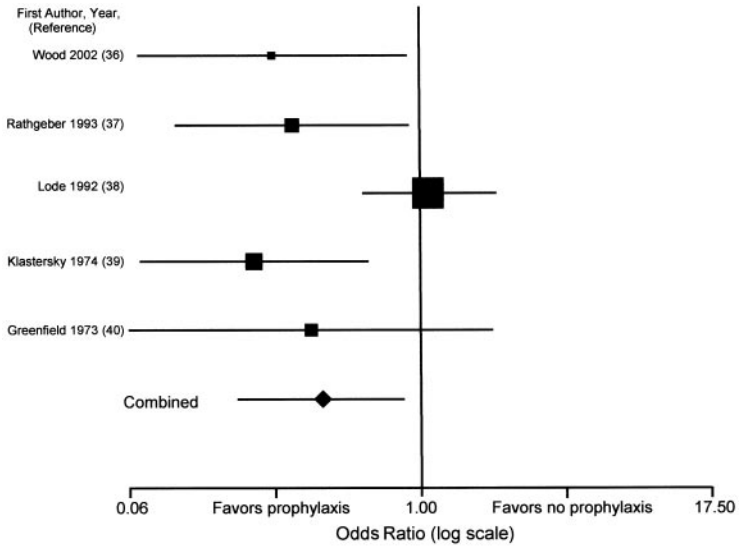

Fig. 1. Meta-analysis of controlled trials of aerosolized antibiotics to prevent ventilator-associated pneumonia. (Adapted from Reference 45, with permission.)

Summary

The rationale for aerosolized antibiotics makes sense, especially when the infection is coating the airways (ie, tracheobronchitis), as opposed to an established inflammatory alveolar process such as pneumonia. Although aerosolized antibiotics can kill airway surface bacteria, the clinical evidence that this approach can treat VAP is negative, and multiple consensus groups recommend against this approach, especially as monotherapy. The clinical evidence for aerosolized antibiotics in preventing VAP is more suggestive, but conflicting. Moreover, there are important concerns about the cost, the development of antibiotic resistance, and other risks, which led several evidence-based consensus groups to recommend against routine use of aerosolized antibiotics for VAP prevention until better data are available. Future studies should probably focus on patients most at risk for VAP (eg, evidence of new tracheobronchitis) and limit therapy to targeted antibiotics given for as short a period as possible. We also must identify which of the minimum-inhibitory-concentration/area-under-the-curve medications (aminoglycosides and quinolones) are most likely to be effective, when they should be started, in which patients, at which dose, and for how long. Although it is very possible that aerosolized antibiotics may become a mainstay in preventing VAP in the future, data are too few to support their routine use at this time.

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Discussion

Deem: Neil, you're leaning against inhaled antibiotics for treating VAP, but it seems that you're leaning that direction only because of lack of evidence. What is your concern? Are you also arguing against inhaled antibiotics for VAP in concept? Do you think inhaled antibiotics are going to have a role in the treatment of VAP? And would you *never* use inhaled antibiotics for VAP if the patient had a multiple-drug-resistant organism?

MacIntyre: I conveniently avoided the whole discussion of trying to defend *treatment* of VAP in describing the pro position, because—as much as I tried to be a good debater—I could not come up with anything that convinced me that treating VAP with inhaled antibiotics is a good idea. Does anybody here have some data that can convince me otherwise?

Rubin: Now that we are away from the debate format, I agree with Neil, as usual. However, there may be use in treating multiply-resistant organisms—not as a monotherapy, but as an adjunct to intravenous antibiotics, in selected patients. And I would do it in the context of an appropriate trial. Because very high levels of antibiotics are achievable, one of the things we've done in CF therapy is to use several drugs at high doses for a long time, recognizing that, although there is a lot of junk in the airways, dead bugs don't reproduce, and if they don't reproduce they don't develop resistance. So there may be a role in decontaminating the proximal airway, but there are no data on that now. The data are clearly strongest for preventing VAP.

Branson: Neil, I think it's how you frame the question. We clearly see trauma patients who have the clinical signs of VAP, probably from aspiration at the scene, but whose distal lung samples don't show pneumonia, but they do have fever or high white-cell count and copious secretions. I think those are probably patients with tracheobronchitis, in whom we sometimes say they have pneumonia, but there is no new infiltrate, and it's hard to see around their pulmonary contusion. I think those patients actually may be ideal for inhaled antibiotics.

MacIntyre: I've been working on advising some companies about developing inhaled antibiotics for those kinds of patients, and the companies have had a great deal of difficulty convincing the FDA [Food and Drug Administration] of this entity called "tracheobronchitis." That's unfortunate, because for this concept to work you need to treat the infection early, while it is still on the surface and reachable by an aerosol. I think tracheobronchitis describes that situation relatively well, but the FDA said, "No, we can't give you an indication for tracheobronchitis. You have to go for an indication in a more traditional pneumonia sense." I'm hoping that can be negotiated, because I'm not sure that's the right way to be going.

Fessler: One of the problems I have with the data in this field is that the diagnosis of VAP is so difficult and often requires quantitative sputum cultures, but if you suction sputum from the airway and it mixes with the colistin that's coating the proximal airway, the laboratory will probably find that the bacteria count is below the threshold that makes the VAP diagnosis. Is that what we're seeing in the data that shows a reduction in VAP but no difference in mortality?

MacIntyre: That certainly could be, if you contaminated the sample with the antibiotic in the airway. That's a limitation of these studies. But it's more than just quantitative cultures that describe VAP. These scores include infiltrates, fever, and white-cell count. But you're right that it's a methodologic flaw in the diagnosis and may create a bias.

Pierson:* It seems to me that there are 2 basic issues that we are discussing at the same time. One is the prevention of VAP. The other is the treatment of VAP. And then, within each of those there seem to be 2 basic issues: aerosolized antibiotics alone, and aerosolized antibiotics *with* systematic antibiotics. It seems to me that it ought to be made very clear when we are considering this issue, as well as when we are reading the literature, which of these categories we are talking about. I see patients with clinically diagnosed VAP treated with aerosolized antibiotics alone. Any comment on that?

MacIntyre: We do not routinely use aerosolized antibiotics for VAP, or even for tracheobronchitis, although I would very much like to see a systematic study of that. Some of the companies I have worked with advocate that, but we don't do it routinely. Do you do that in Seattle?

Pierson: No. We see it requested, and we sometimes see it get started, and then we have big debates about it. But I've always held that topical treatment of an established clinical infection has not been shown to be effective.

MacIntyre: I would agree with that. Ira, in your pediatrics unit, do you do this differently than we do?

Cheifetz: Except with CF patients, we never use inhaled antibiotics to prevent or treat VAP, so to me it is interesting that this is even a debate, because in our pediatric ICU this is never an issue.

Rubin: Dave, I agree with you. Not only are there no data to support the *sole* use of inhaled antibiotics, there are no data to support their *adjunctive* use either. But there is a theoretical basis, from animal models, for using them to treat established VAP, and I think there is a strong theoretical basis for decontamination, not only of the upper airway but of the whole tracheobronchial tree in the patients most likely to get VAP because of prolonged mechanical ventilation. But *absolutely not* for treating VAP! I think it would probably be unethical to do a clinical trial using only inhaled antibiotics for treating established VAP.

Pierson: The context in which I've observed this being brought up as a possible therapy, and sometimes used, is in ICU "adventurism," which takes us back to our first discussion. "This patient looks like they're not making it; they're deteriorating; they have persistent *Pseudomonas* or other resistant infection. Let's just add in the aerosolized antibiotics, because that might help."

Deem: I've probably been one of those offenders. I can recall a patient who had a VAP that was resistant to every antibiotic except aminoglycoside, but he had a creatinine of 3 or 3.5 mg/dL, so we didn't want to use aminoglycoside. We used aerosolized tobramycin, I believe, in addition to another agent that it was resistant to, and he recovered. So, anecdotally, we got a response. But it gets back to the debate about when it is appropriate to use unproven therapies. I think that was an appropriate use of an unproven therapy. Whether we would have gotten the same outcome without aerosolized tobramycin I'm not sure.

Hess: I think a big problem, as far as designing a clinical trial, is standardizing the dose, because it is very difficult to come up with a standard dose when delivering aerosol during mechanical ventilation. And even if you could do that in the clinical trial, my bigger concern would be that when that gets rolled out to widespread use, the dosage could be highly variable because of different nebulizers, different ventilator settings, and so forth.

Steinberg: Regarding aerosolized antibiotics for VAP prevention, as opposed to VAP treatment, presumably if they were proven efficacious we'd be using them on a much wider scale, treating many more patients. We may not create resistance in individual patients, because we are only using them for a short period of time, but aren't we setting the stage for creating widespread resistance in our units by selectively eliminating susceptible bacteria, and allowing the growth of the resistant ones? I would really worry about that.

Rubin: This may be an indication for "crop rotation," as Kollef calls it. It takes a lot of microbial energy to develop resistance. *Pseudomonas* has a big genome and *Burkholderia* has 4-ring chromosomes, much of that devoted to efflux pumps and other means of resistance. It's a bit like a knight out on the battlefield. If you're covered in armor, you're safe, but if you don't take the armor off afterwards, you're going to have a hard time getting a date on a Saturday night, and for bacteria, reproduction is the name of the game. So as soon as you remove antimicrobial pressure, you drop those resistance factors. And if you hit them with a different antimicrobial, it may be that crop rotation would be best suited for prophylactic use. Tobramycin is available. Gentamicin is being made available. Cipro is being reformulated. Aztreonam and colistin are fine. There are another twelve or fifteen in development. So it may be useful for prevention.

Steinberg: And presumably with crop rotation you would shift classes, not just specific agents. Is that right?

Rubin: That's what's been advocated.

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