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Enhancement of lung levels of antibiotics by Ambroxol and Bromhexine

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Abstract

Introduction: Major unmet needs remain for improved antibiotic treatment in lung infections. While development of new antibiotics is needed to overcome resistance, other approaches to optimize therapy using existing agents are also attractive. Ambroxol induces lung autophagy at human-relevant doses and improves lung levels of several approved antibiotics.

Areas covered: This review discusses preclinical and clinical studies of the effects of ambroxol (and its prodrug precursor bromhexine) co-treatment upon levels of antibiotics in lung tissue, sputum and bronchoalveolar lavage fluid.

Expert opinion: Ambroxol co-treatment is associated with significant increases in lung tissue and airway surface fluid levels of a range of antibiotics including beta lactams, glycopeptides, macrolides, nitrofurans and rifamycins. In most cases, the increased levels are only modest and are insufficient to overcome high-level resistance against that same antibiotic class, and so co-treatment with ambroxol is unlikely to alter clinical outcomes. Additionally, for most antibiotics there is no evidence that outcomes in non-resistant disease are improved by higher drug levels, and there is limited efficacy of co-treatment of antibiotics with ambroxol for most pathogens. The two cases where ambroxol may improve therapy are rifampin-sensitive tuberculosis and non-tuberculous mycobacterial infection, and vancomycin sensitive methicillin resistant *Staphylococcus aureus* pneumonia.

Keywords

Lung pharmacokinetics; antibiotic resistance; autophagy

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Declaration of interest

GS Timmins is co-founder and major stock holder of SpinCeutics Inc. (Santa Fe NM), a company that licenses deuterated ambroxol intellectual property from the University of New Mexico, and is developing this compound for use in treatment of NTM lung disease, and could benefit financially through stock ownership. GS Timmins and V Deretic are co-inventors of the deuterated ambroxol intellectual property, and could also benefit from royalty payments. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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1. Introduction

Ambroxol is the active metabolite of the prodrug bromhexine, and both are widely approved as over the counter expectorant medicines with excellent records of safety.[1] It was recently shown that both drugs induce the fundamental process of autophagy,[2, 3] although for human-approved doses this activity is probably only important for ambroxol, because of the lower approved doses of bromhexine (16 mg three times daily, TID versus 30mg TID for ambroxol) and the relatively low efficiency of conversion of bromhexine into ambroxol. Accordingly, it was shown that that human-relevant levels of ambroxol potentiated macrophage killing of *Mycobacterium tuberculosis*, but when used with rifampin in mice, the effect of adding ambroxol was many orders of magnitude greater than when used alone in cells.[2] Since rifampin activity is usually limited by low dosing,[4] we hypothesized any ambroxol-mediated modulation of lung pharmacokinetics (PK) of rifampin could result in this effect, and searched the literature for reports of this activity. Reports showed that in a rat model, ambroxol co-administration enhanced the half-life of ambroxol in lung tissue leading to increases in rifampin levels lung,[5] and that in mice a two-fold increase in maximum concentrations (C_{max}) and 80% increase in the area under the curve (AUC) were observed. [6] Since desired lung levels of rifampin are rarely achieved with conventional doses for either tuberculosis (TB)[4] or non-tuberculous mycobacteria (NTM),[7] ambroxol may enable attainment of target rifampin levels in the lung to enhance clinical therapy.

However, searching revealed that many more antibiotics than rifampin had their lung levels improved by ambroxol and bromhexine, and we report the preclinical (Table 1) and clinical (Table 2) literature, and evaluated any improvements in relation to their likelihood to enhance therapy of both drug sensitive and drug-resistant infections. In most preclinical studies, whole lung tissue levels are reported, but clinically most studies report less invasive measures such as sputum (essentially equivalent to pus coming from the sites of infection), or bronchoalveolar lavage (BAL) fluid. To enable preclinical-clinical dose comparison, ambroxol plasma C_{max} are similar when humans are treated on a mg/patient basis and rodents are treated with the same amount but on a mg/kg body weight basis, *i.e.* a human 30 mg dose achieves similar C_{max} to a 30mg/kg dose in rats.[8] While lung tissue levels are readily measured directly in animal model studies, the collection of human lung tissue biopsies required for these is more problematic, and so most clinical studies used less invasive sampling procedures such as bronchoalveolar lavage (BAL) and sputum collection. Although BAL and sputum antibiotic levels are relevant measures for infections of the lung lumen, they are meaningfully different matrices from the whole lung tissue used in most animal studies, and so direct comparisons are difficult. Our strategy was to use Pubmed and Google Scholar using either ambroxol or bromhexine as one term, and each of the following as the other: antibiotic* or antibacterial* or antimicrobial* or antimycobacterial* or lactam or quinolone* or fluoroquinolone* or macrolide or aminoglycoside* or tetracyclin*. Papers were included from these searches that we could obtain full text of, that contained quantitative data upon antibiotic levels in the lung or lung-derived samples, and that did not have other confounding interventions or treatments in addition to the two drugs.

2. Effects of ambroxol and bromhexine on various airway levels of antibiotics

2.1 Beta lactams

Preclinical studies by Wiemeyer used rats treated with 50 mg/kg oral ampicillin and amoxicillin with or without 10mg/kg oral ambroxol, equivalent to a relatively low human dose.[9] The lung tissue concentrations of ampicillin and amoxicillin were increased by 23% and 27% with ambroxol. Imaoka studied mice treated with 30 mg/kg oral ampicillin or cephalexin, and found that lung levels were not significantly increased by 1 mg/kg dose of ambroxol, although this does represent a low ambroxol dose.[6] Matsuda *et al* showed that in horses given 0.68mg/kg oral ambroxol BAL fluid cefalothin was increased by about 50%, but only when cefalothin/BAL protein ratios were measured, raw cefalothin levels in micrograms/ml were unchanged by ambroxol.[10] Clinically, Taskar *et al.* measured sputum levels, and showed that the mean amoxicillin levels in sputum from patients treated with 500 mg amoxicillin were increased from 0.272 µg/ml to 0.674 µg/ml when 8mg bromhexine was added.[11] In contrast Bergogne-Berezin *et al.* found no increase in bronchial secretion levels of amoxicillin with either 48 or 96 mg bromhexine daily.[12] Gene *et al.* treated patients with 1000mg oral amoxicillin TID with and without 60 mg oral ambroxol TID, and found the mean levels of amoxicillin in BAL fluid were increased from (0.19 +/- 0.02 micrograms/ml to (0.32 +/- 0.02 micrograms/ml by ambroxol.[13] Spatola *et al.* conducted a similar trial to Gene *et al.* but measured amoxicillin in resected lung tissue, and although only a trend to increased amoxicillin was observed in the ambroxol group, the mean lung to serum concentration of amoxicillin ratio was significantly increased from 0.41 to 0.672 by ambroxol.[14] Paganin *et al.* studied patients treated with 200 mg ofloxacin bid with and without 30 mg ambroxol TID, with no significant increase in BAL levels being observed, although ofloxacin levels in alveolar cells recovered from BAL were three fold higher with ambroxol.[15] Liu *et al* studied patients treated with 100 mg cefixime twice daily (BID) with or without 60 mg ambroxol TID, and found mean BAL levels of cefixime were increased from 0.022 mg/l to 0.037 mg/l.[16]

Most of the studies examined found relatively moderate improvements in lung levels of beta lactams by ambroxol, ranging from 23% to 68% increases, with only the study of Taskar *et al.* using bromhexine showing a larger effect (148%).[11] Three studies reported no significant effects: while Paganin *et al.* did not report any positive findings, Imaoka reported the same low ambroxol dose significantly potentiated rifampin lung levels, while Bergogne-Berezin *et al.* who reported that a lower bromhexine dose did potentiate lung erythromycin levels. Clinical outcomes were only reported by Taskar *et al.* and although patient and physician reported responses showed improvement, this was not seen in radiological or bacteriological outcomes.[11] Since minimum inhibitory concentration (MIC) breakpoints for beta lactam resistance have at least a 2 fold difference between sensitive and resistant bacteria, data from most of the studies would not support treatment of beta-lactam resistant disease with a beta lactam-ambroxol combination, as the increase would not overcome the level of resistance. For beta lactam- sensitive disease, the time over the MIC is best associated with bacterial eradication,[17] however none of the studies reported detailed pharmacokinetics and so it is not possible to determine if ambroxol co-therapy might result

in better eradication rates in beta lactam sensitive pneumonias, although this remains possible.

2.2 Macrolide and nitrofurans

Preclinical studies in rats treated with 50 mg/kg oral erythromycin with or without 10mg/kg oral ambroxol, showed lung tissue concentrations were increased 27% by ambroxol.[9] In rats treated with roxithromycin (10 mg/kg) the addition of ambroxol (2 mg/kg) increased mean lung tissue roxithromycin levels from 3.20 to 4.06 µg/ml.[18] In a complimentary study in rats, Lee and Choi showed that 10mg/kg clarithromycin increased the bioavailability of a 12 mg ambroxol dose by 71%,[19] presumably through its actions as an inhibitor of cytochrome P450 3A4, an important enzyme in ambroxol metabolism.[20] The effect of ambroxol on lung clarithromycin levels was not reported however. Bergogne-Berezin *et al.* reported that in patients treated with 500 mg erythromycin BID, addition of bromhexine (8 mg TID) led to an increase in the bronchial secretion/serum ratio of erythromycin from 0.24 to 0.434.[12]

In chickens treated with 50 mg/kg of furaltadone, either bromhexine or ambroxol were administered at 0.875 and 1.75 mg/kg with a furaltadone only control group. Ambroxol led to dose dependent increases in tracheobronchial secretion furaltadone levels from 3.1, to 5.6 and 7.2 mg/g respectively, while both doses of bromhexine led only to an increase from 3.1 to 3.9 mg/g. [21] This paper was the only one that directly compared the effects of bromhexine with those of ambroxol, and supports the earlier assertion that achieving significant effects in humans are more likely to be achieved with ambroxol.

Overall, the increases in lung levels of macrolides by ambroxol were modest, and unlikely to enable treatment of macrolide-resistant lung infections with a macrolide-ambroxol combination. The effects of ambroxol on lung levels of furaltadone were larger, although the clinical significance of this finding in an antibiotic that is only approved for veterinary use is unclear. Since furaltadone has significant structural similarity to other oxazolidinone antibiotics such as linezolid, similar increases in lung drug levels by ambroxol might occur. This could prove beneficial in allowing the use of lowered doses linezolid in diseases such as multi-drug resistant tuberculosis, as linezolid toxicity is common and associated with cumulative dosage used.[22]

2.3 Rifamycins and glycopeptides

Imaoka reported that in mice given 50 mg/kg rifampin PO, co-administration of 1mg/kg ambroxol increased the rifampin C_{max} in lung tissue from 9.48 to 22.47 µg/ml at 4 hours, and increased the AUC_{0-24h} from 99 µg*h/l to 178 µg*h/ml. Zhang *et al.* reported that in rats IV treated with 30 mg/kg rifampin, mean lung levels at 1, 2 and 4 hours were 31.8, 15.2 and 6.2 µg/ml, the lung levels of rifampin were increased by 15 mg/kg IV ambroxol pretreatment to 35.5, 25.6 and 13.6 µg/ml at the same time points, leading to significantly greater rifampin retention within the lung that could lead to a higher AUC.

Choi *et al.* reported the antimicrobial activity of rifampin (10mg/kg/day) against *M. tuberculosis* in a mouse model of infection, where the addition of ambroxol (16 mg/kg/day) led to over 170 fold decrease in mean lung bacterial numbers compared to rifampin alone

after 4 weeks of treatment. Because of inter-animal variation, median values are often useful, and at 4 weeks the median cfu/lung decreased from 420,000 to 256 with ambroxol, while at 6 weeks ambroxol decreased median cfu/lung from 400 to 7. Thus, ambroxol at a human relevant dose, led to meaningful increases in the antimycobacterial effects of rifampin.

Clinically, Imaoka also reported a very limited data set of three patients treated with 450 mg rifampin, who acted as their own controls and were also treated with 450 mg rifampin and 15 mg ambroxol, and the concentration of rifampin in sputum measured. The AUC_{0-24h} of rifampin in these patients was increased by ambroxol from 3.0 to 6.4 mg*h/l in patient 1, from 4.7 to 30.7 mg*h/l in patient 2, and from 3.0 to 4.1 mg*h/l in patient 3. Total sputum output of rifampin was also increased by ambroxol, from 3.1 to 11.6 µg inpatient 1, from 3.0 to 20.8 µg in patient 2, and from 2.7 to 10.2 in patient 3.

All studies found robust and significant effects of ambroxol upon rifampin levels or effects, including many increases over 100%, and at human-relevant doses. Unfortunately, given the very high MICs of rifampin resistant TB,[23] it is unlikely that addition of ambroxol to standard rifampin doses would be effective in treatment of rifampin resistant TB. However, it is well known that rifampin is significantly under dosed in sensitive mycobacterial disease, both in TB[4] and in NTM[7], despite higher levels being associated with improved cure rates. For example in *M. avium* complex infections, standard 600 mg daily dosing of rifampin led to desirable pharmacokinetic outcomes (AUC/MIC) for only 6-18% of 531 patients treated at National Jewish Health, Denver.[7] Therefore, co-administration of ambroxol with rifampin could lead to greatly improved outcomes in NTM disease, without exposing patients to the increased risk of drug toxicities from higher dose rifampin. In TB, the situation is less clear, as unlike NTM which is only found in lung tissue, TB disseminates to many organs such as spleen, and the effects of ambroxol on rifampin levels in these tissues has not been reported. The effects of ambroxol are not known on other rifamycins, such as rifabutin, but should they be similar use of ambroxol could allow increased rifabutin levels to treat *M. abscessus* disease,[24] an area of great clinical need that is limited by rifabutin toxicity.

There is only one report of the effects of ambroxol on glycopeptide lung levels, a clinical study by Chen *et al.* of vancomycin levels in sputum of patients with methicillin resistant *Staphylococcus aureus* (MRSA) lung infection.[25] Patients were treated with 1g vancomycin IV BID, with or without 60 mg ambroxol IV BID, and the mean sputum concentration of vancomycin increased from 1.80 to 3.57 µg/ml. There was no report of outcomes. It is uncertain whether this might lead to the ability to treat vancomycin resistant *S. aureus* (VRSA). However, it is well known that penetration of vancomycin from plasma into the lung epithelial lining fluid (ELF), the site of infection is suboptimal, with a median ELF/plasma ratio of only 0.39 being reported,[26] and leading to sub-optimal treatment of MRSA pneumonias with MIC of 1 mg/l. However, because of the higher risks of toxicity of higher vancomycin doses,[27] it is not possible to escalate dose any further and co-administration of ambroxol with vancomycin might significantly improve patient outcomes with MRSA.

3. Conclusions

Bromhexine and ambroxol lead to increases in the lung levels of a wide range of antibiotics including beta lactams, erythromycin, rifampin and vancomycin, with at least one clinical report for each class. No reports of such increases were found for any aminoglycosides, fluoroquinolones, sulfonamides or tetracyclines, although it is unclear if this is due to biased non-reporting of negative data, or a lack of experimentation with these compounds. Effective doses of ambroxol in rodent preclinical models ranged from 1mg/kg to 16 mg/kg, corresponding to C_{max} achieved by relatively low human doses, and so this body of preclinical work represents human relevant ambroxol doses. Clinical studies used from 15mg/day to 180 mg/day total doses of ambroxol and from 8 to 96 mg/day for bromhexine, but neither was dose response explicitly studied, nor is there any clear trend for any dose response, except for a study in chickens.

4. Expert Opinion

It is unlikely that the increases in lung tissue antibiotic levels would be sufficient to allow treatment of organisms deemed resistant to that same antibiotic class, and in the case of most antibiotic-sensitive disease the antibiotic doses used are already clinically effective, and improved outcomes from ambroxol co-treatment are similarly unlikely. In the cases of rifampin treatment of TB and NTM, and of vancomycin treatment of MRSA pneumonia however, the typical doses used are as much limited by drug toxicity as they are guided by clinical effectiveness, and so simply increasing the dose of these antibiotics to increase lung levels is problematic. However, the observed increases in lung levels of rifampin and vancomycin caused by ambroxol occurred without increasing the antibiotic dose, and so could lead to meaningful clinical benefits without increasing dose-related side effects. The use of ambroxol may also help limit development of rifampin resistance. Because of the approved nature of ambroxol, studies to test these hypotheses could be performed relatively quickly when compared to development of entirely new antibiotics. However, significant questions remain, in particular what is the optimal ambroxol dose for use with rifampin or vancomycin. The only report of an ambroxol dose response was in chickens with a veterinary only antibiotic, although a dose response was observed. In moving forwards, the field should address the lack of detailed knowledge of pharmacokinetic effects, especially in humans, and also bacteriological and clinical outcomes.

The case of ambroxol co-administration with rifampin is further complicated by the induction of cytochrome P450 3A4 (Cyp3A4) by rifampin and the sensitivity of ambroxol to Cyp3A4 metabolism.[20] Strategies for overcoming this are: none is needed, use of rifabutin, ambroxol deuteration to resist Cyp3A4, inhibition of Cyp3A4, and high dose ambroxol. Firstly, because the dose response is as yet unknown, it may well be that a typical approved ambroxol dose of 90 mg daily will provide significant benefit, even though much may be metabolized. If this is not so, in some cases it might be possible to replace rifampin with rifabutin (which induces Cyp3A4 to a much lesser extent) such as in treatment of *M. abscessus*. [28] However, it is currently unknown if ambroxol can potentiate rifabutin lung levels, and so this strategy is somewhat more speculative. We have proposed a deuteration strategy to limit Cyp3A4 metabolism of ambroxol and allow more predictable ambroxol

dosing in rifampin treated patients due to variabilities in both rifampin induction of Cyp3A4 and in Cyp3A4 activity.[2] While drug deuteration is a proven strategy for controlling metabolism,[29, 30] deuterated ambroxol would be treated as a new chemical entity by regulatory authorities such as the Food and Drug Administration (FDA), and so would require approval. Inhibition of Cyp3A4 may be a viable strategy, especially in treatment of *M. avium* complex, where the guidelines are for triple therapy using rifampin, a macrolide (azithromycin or clarithromycin) and ethambutol.[31] Since Lee *et al.*[19] showed that clarithromycin significantly inhibited Cyp3A4 to enhance ambroxol bioavailability, use of clarithromycin as macrolide with ambroxol (instead of azithromycin) might offer advantages in ambroxol-enhanced triple therapy through its adventitious Cyp3A4 inhibition. Finally, although clinical use of high doses of ambroxol are reported (1000 mg/day),[32] and might overcome Cyp3A4 induction by rifampin to enable sufficient ambroxol levels, there will also be exposure to higher levels of the Cyp3A4-derived ambroxol metabolites (trans-4-aminocyclohexan-1-ol and 2-amino-3,5-dibromoanthranilic acid and Phase 2 metabolites of these compounds) than in previous reports of high dose ambroxol. The effects of increased levels of these metabolites are unknown. Overall, there are a range of strategies to overcome rifampin induced Cyp3A4-mediated ambroxol metabolism, with ample opportunity for clinical trial. Since rifampin combination therapy has been used in non-mycobacterial lung disease, such as in *Legionella* pneumonia, and ambroxol co-treatment may show potential in these cases also. [33]

The only therapeutic study examined was of *M. tuberculosis*, which is an intra-cellular pathogen in which autophagy plays a major antibacterial role.[34] Since ambroxol also induced lung autophagy,[2] its effects might be optimal for other intracellular autophagy sensitive pathogens such as *M. abscessus* [28] as autophagy inhibition with azithromycin use in cystic fibrosis is associated with acquisition of this severe pathogen. Ambroxol alone may have a role in preventing *M. abscessus* in cystic fibrosis, and may be combined with rifabutin in treatment. However, in lung infections caused by organisms not controlled by autophagy, it remains to be determined how much effect modulation of lung levels alone by ambroxol will affect treatment outcome. It is important to note that the autophagy induced in lung by ambroxol might significantly control inflammation in lung infection, independent of any antimicrobial effects, and this should receive attention. The other major question to be resolved include determining the mechanism(s) by which ambroxol can enhance lung levels of antibiotics, as once identified this target might lead to new drugs with optimized effects, and determining what other antibiotics can have their lung levels increased by ambroxol, leading to meaningful clinical benefits.

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Table 1.

Effects of ambroxol or bromhexine administration with antibiotics in preclinical models. PO, oral; IV, intravenous.

Antibiotic and dosing	Ambroxol/Bromhexine Dosing	Outcome measure	Study
Amoxicillin, 50 mg/kg PO	Ambroxol 10 mg/kg PO	27% increase in rat lung tissue level of amoxicillin	Wiemeyer[9]
Ampicillin 50 mg/kg PO	Ambroxol 10 mg/kg PO	23% increase in rat lung tissue level of ampicillin	Wiemeyer[9]
Ampicillin 30 mg/kg PO	Ambroxol 1 mg/kg PO	No increase	Imaoka[6]
Cephalexin 30 mg/kg PO	Ambroxol 1 mg/kg PO	No increase	Imaoka[6]
Cefalothin 22.8 mg/kg IV	Ambroxol 0.68 mg/kg PO	No increase in µg/ml in BAL fluid from horse. When presented as µg cefalothin/µg BAL protein a 50% increase was seen.	Matsuda <i>et al.</i> [10]
Erythromycin 50 mg/kg PO	Ambroxol 10 mg/kg PO	27% increase in rat lung tissue level of erythromycin	Wiemeyer[9]
Clarithromycin 10 mg/kg PO	Ambroxol 12 mg/kg PO	71% increase in ambroxol bioavailability in rat	Lee and Choi[19]
Roxithromycin 10 mg/kg PO	Ambroxol 2mg/kg PO	27% increase in rat lung tissue roxithromycin at 6 h	Wang <i>et al.</i> [18]
Rifampin 30 mg/kg IV.	Ambroxol 15 mg/kg IV	74% and 188% increase in rat lung tissue rifampin at 2 and 4 h	Zhang <i>et al.</i> [5]
Rifampin 50 mg/kg PO	Ambroxol 1mg/kg PO	137% increase in maximal mouse lung tissue rifampin and 80% increase in AUC _{0-24h}	Imaoka[6]
Rifampin 10 mg/kg/day PO	Ambroxol 16 mg/kg/day PO	170 fold lower cfu/lung after 4 weeks	Choi <i>et al.</i> [2]
Furaltadone 50 mg/kg PO	Bromhexine 0.875 and 1.75 mg/kg/day PO	26% increase in tracheobronchial furaltadone in chicken	Sumano <i>et al.</i> [21]
Furaltadone 50 mg/kg PO	Ambroxol 0.875 and 1.75 mg/kg/day PO	81 and 132% increases in tracheobronchial furaltadone in chicken	Sumano <i>et al.</i> [21]

Table 2.

Clinical effects of ambroxol or bromhexine administration with antibiotics in preclinical models. PO, oral; IV, intravenous; QD, once daily; BID, twice daily, TID three times daily.

Antibiotic and dosing	Ambroxol/Bromhexine Dosing	Effect on Antibiotic Levels	Study
Amoxicillin 500 mg PO QD	Bromhexine 8 mg PO QD	148% increase in sputum amoxicillin	Taskar <i>et al.</i> [11]
Amoxicillin 1000 mg PO BID	Bromhexine 16 and 32 mg PO TID	No significant effect seen in bronchial secretions.	Bergogne-Berezin <i>et al.</i> [12]
Amoxicillin 1000 mg PO TID	Ambroxol 60 mg PO TID	68% increase in BAL amoxicillin	Gene <i>et al.</i> [13]
Amoxicillin 1000 mg PO TID	Ambroxol 60 mg PO TID	64% increase in lung tissue/serum ratio	Spatola <i>et al.</i> [14]
Ofloxacin 200 mg PO BID	Ambroxol 30 mg PO TID	No increase in BAL ofloxacin, 3 fold increase in alveolar cell ofloxacin	Paganin <i>et al.</i> [15]
Cefixime 100 mg BID	Ambroxol 60 mg TID	68% increase in BAL cefixime	Liu <i>et al.</i> [16]
Erythromycin 500 mg PO BID	Bromhexine 8 mg PO TID	80% increase in erythromycin bronchial secretion/ blood ratio	Bergogne-Berezin <i>et al.</i> [12]
Vancomycin 1g IV BID	Ambroxol 60 mg IV BID	98% increase in sputum vancomycin	Chen <i>et al.</i> [25]
Rifampin 450mg PO	Ambroxol 15 mg PO	Mean 230% increase in sputum rifampin AUC ₀₋₂₄	Imaoka[6]