Long-term antibiotics in the management of non-CF bronchiectasis—do they improve outcome?

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Summary In addition to bacteria and inflammatory cells, the sputum of patients with bronchiectasis contains mediators that damage the airway epithelium and promote inflammatory change. The deleterious effects of these mediators, such as neutrophil elastase, reduce host defences and consequently perpetuate the propensity to recurrent infection. This 'vicious cycle' of infection and inflammation in bronchiectasis suggests that long-term antibiotic therapy might be beneficial in these patients by reducing microbial load and, in doing so, inhibit inflammation in the lung allowing tissue repair to occur. Short courses of antibiotics achieve clinical improvements and also have been shown to reduce the levels of harmful mediators in the sputum. This article will cite the studies reported for long-term antibiotic treatment in bronchiectasis and overall there seems to be benefits for patients with chronic sputum purulence. The evidence that supports the postulated pathological mechanisms will also be discussed. Important issues in clinical practice such as the usefulness of antibiotic sensitivities, the evolution of resistance patterns, and drug delivery will also be discussed.

Introduction

Bronchiectasis is a chronic lung disease associated with permanent dilatation of the bronchi and usually excess mucopurulent secretions.^1^ Many individuals with this disorder endure significant impairment in their quality of life due to persisting cough with sputum production, dyspnœa, constitutional upset, and infective episodes. Whilst it is possible to have a normal life expectancy with bronchiectasis,^2^ at times exacerbations of the condition can be sufficiently severe as to be life threatening and a number of patients experience accelerated loss of lung function and progress to respiratory failure and premature death.^3^

The effectiveness of antibiotics in the treatment of acute infective exacerbations of this condition is established^4^—^6^ although patients often require higher than standard doses.^7^ Short courses of antibiotics result in both a reduction in sputum volume as well as clearing of purulence.^5^ Patients report improvements in general health and, in parallel, there are favourable changes in markers of infection such as temperature, white cell count, and serum inflammatory indices. In contrast, the benefits of long-term antibiotic treatment in bronchiectasis are a lot less clear cut. One would anticipate that this treatment strategy would benefit patients in various ways including suppression of symptoms, a reduction in exacerbation rates and improved quality of life. Furthermore, if antibiotics influenced the pathological processes that led to disease progression, then long-term treatment might conceivably alter the natural history of the condition. This might be particularly important for the group of individuals with severe disease and deteriorating pulmonary function.
Conversely, there is a widely held view that antibiotics used in this way may promote resistance patterns amongst colonising organisms. This review will discuss the theoretical rationale for the use of long-term antibiotics in bronchiectasis and the clinical evidence that exists.

### A potential mechanism for long-term antibiotic treatment

The pathogenesis of the airway dilatation and destruction is complex. Although there are numerous predisposing conditions, an underlying cause may be impossible to identify and idiopathic bronchiectasis constitutes approximately half of the cases seen. Regardless of the aetiology, characteristic pathophysiological changes are seen in the lung and these include excess mucus production and impaired mucociliary transport. The epithelial lining shows loss of columnar ciliated cells, an inflammatory cell infiltrate and occasional ulceration. The loss of normal mucosal integrity and a fully functioning mucociliary escalator may be the initiating event which allows microbial colonisation of the airway and in turn generates an inflammatory response. Further damage to the airway epithelium weakens host defences and perpetuates a continuum of infection, inflammation and progressive damage to the lung. End-stage bronchiectatic lung shows gross destruction to the airways as well as chronic fibrotic change. Any therapeutic intervention in bronchiectasis should be designed to break or weaken the link between infection and inflammation. A reduction in both the number of acute infections and the microbial load in the lung should result in a diminution in inflammatory cell influx and tissue damage and eventually allow healing. These processes are collectively described by the Vicious Cycle hypothesis and this is the basis of the case put forward by protagonists for long-term antibiotics.

The chronic expectoration of purulent or mucopurulent sputum by individuals with bronchiectasis is central to the understanding of effective management strategies, including long-term antibiotics. Sputum often reveals evidence of both infection and inflammation. Positive microbiological cultures for bacteria such as *Haemophilus influenzae* and *Pseudomonas aeruginosa* are direct evidence of ongoing colonisation/infection in the lung and may inform decisions regarding the antibiotic treatment of acute exacerbations. Perhaps more relevant to the issue of long-term antibiotics is the presence in the sputum of markers of inflammation. Serum proteins, including albumin, are found in the sputum of these patients and the sputum/serum albumin ratio is a correlate of airway inflammation in bronchiectasis. In addition proteinases, such as neutrophil elastase, superoxide radicals, and inflammatory cells are found in the sputum and are also surrogate indices of inflammation and ongoing damage. Purulent secretions contain high levels of these factors and the positive correlation between neutrophil elastase and albumin concentrations indicates the association of pus with bronchial wall inflammation.

Neutrophil elastase is a serine proteinase and stimulates mucous gland hyperplasia, as well as damaging ciliated epithelial cells. It is also postulated that high levels of neutrophil elastase may directly promote microbial colonisation. This effect is mediated via detrimental actions on the function of IgA (allowing bacterial adherence) and also on IgG (failure to fix complement).

Proof of the role of these pro-inflammatory mediators in bronchiectasis would be strengthened if measurable clinical improvements were to coincide with a transformation of sputum from chronic purulence to mucoid following treatment. Stockley et al. showed such a change in a group of 15 patients treated with antibiotics, taken during a stable phase for 14 days. Twelve of 15 patients treated with amoxycillin, co-trimoxazole, or tetracycline showed macroscopic clearance of their sputum from purulent to mucoid and associated reductions in the elastase activity. In parallel with these changes, there were significant reductions in the sputum/serum albumin ratio indicative of improvements in the levels of bronchial inflammation. Four patients ceased to expectorate any sputum during the course of antibiotic treatment. All patients showed a return of sputum purulence and elastase activity within 1 week of stopping treatment.

A further study by the same group showed benefits in favour of prolonged antibiotic treatment (over 4 months) in a group of bronchiectatic patients with chronic purulent elastase positive expectoration. Ten patients received amoxycillin (250 mg t.i.d., 3 g b.i.d., or nebulised 500 mg in 5 ml sterile water b.i.d.). Despite seven patients’ sputum cultures suggesting amoxycillin-resistant organisms, all 10 individuals demonstrated a transition to mucoid (or mucopurulent) sputum during the course of treatment. In parallel with this, there were improvements in patients symptom scores (well being and cough), sputum volume and systemic inflammatory markers (acute-phase serum proteins). As with the previous study, there were significant falls in sputum neutrophil elastase and
sputum/serum albumin ratios. Following the termination of antibiotic treatment, the elastase and sputum/serum albumin ratio rose again to near pre-treatment levels. In addition, the authors also demonstrated a chronic systemic inflammatory state in ‘stable’ bronchiectasis compared with healthy controls, as measured by serum \( \gamma_1 \)-antichymotrypsin levels. This was most marked in patients with chronic purulent sputum.

A previous clinical trial evaluating the benefits of antibiotic treatment in bronchiectasis showed similar results to the aforementioned studies, indeed the data helped inform the hypothesis relating to sputum markers and ongoing inflammation. In this non-randomised study, Hill et al. showed that patients with mucoid sputum responded well to short courses of conventional dose amoxycillin for exacerbations, but that patients with mucopurulent or purulent sputum required higher doses over a longer period. About 60% of the patients with purulent sputum responded to amoxycillin 3 g b.i.d. (compared to 17% when treated with 250 mg t.i.d.). A further group of patients failing to respond to high-dose oral treatment showed improvements on nebulised amoxycillin over 4 months. Despite appearing to be clinically stable prior to treatment, the patients in the mucopurulent and purulent groups reported improvements in well being and symptoms. After treatment, mucopurulence and purulence returned rapidly in these patients. The authors discuss the importance of dose and the relevance of tissue/sputum penetration in cases with chronic purulence. They emphasise the need to exceed the mean inhibitory concentration for organisms colonising the lung and found little correlation between in vitro sensitivity testing and clinical response.

A further study by Ip et al. reported changes in sputum neutrophil chemotactic activity (NCA) and elastase-like activity (EA) amongst a group of 12 bronchiectatic patients with acute exacerbation treated for 2 weeks with antibiotics. All were chronic purulent sputum producers and were followed up at 2 and 6 weeks after treatment. They showed a significant increase in NCA and EA during exacerbation which returned to normal within 1 week of antibiotic treatment. In parallel with this there were clinical responses. The second week of antibiotics did not result in a further fall in NCA or EA. At 2 and 6 weeks, the inflammatory markers remained at the same level as they had been at baseline prior to the exacerbation. The authors concluded that acute antibiotic treatment was of benefit but were unable to show that this treatment resulted in any improvement in chronic airway inflammation. All the 12 patients were noted to expectorate mucopurulent or purulent secretions.

**Clinical trial evidence**

Compared with other respiratory disorders, there are relatively few trials looking at the use of long-term treatment with antibiotics in bronchiectasis. A recent summary of systematic reviews carried out by the Cochrane Collaboration examining randomised controlled trials in the treatment of airway diseases found 68 reviews derived from 641 trials. When broken down by disease there were only six reviews dealing with bronchiectasis compared with 33 for asthma. The patient base for the asthma reviews numbered 26,680 subjects, the figure for the bronchiectasis reviews was 181. Clearly, asthma is a more common disorder; however, these statistics demonstrate the shortfall in controlled data for bronchiectasis and limits the evidence base from which guidelines for disease management can be drawn. Acknowledging the paucity of data, do the existing studies examining the use of long-term antibiotic treatment allow us to draw any conclusions about possible benefits and risks? The trial results on which we must make these decisions are described.

The first study, albeit not a randomised controlled trial, looking at the use of long-term antibiotics was published in 1952. Harris et al. studied 62 patients, 38 of whom suffered from bronchiectasis. Patients received chloramphenicol 1 g b.i.d. or t.i.d. for between 2 and 6 months. Thirty-six of the 38 bronchiectasis patients experienced sustained reductions in their sputum volume by 50% or more. Following this period, the antibiotic was stopped and 14 patients went on to take placebo, the remainder discontinued all treatment. Relapse of symptoms occurred within 3 months of stopping the antibiotic regardless of whether the subjects had gone onto placebo.

The following year, the use of chlortetracycline 250mg b.i.d. was reported by McVay et al. Twenty-nine patients (not all of whom were bronchiectatic) were allocated, non-randomly, to receive antibiotic (20 patients, for a mean of 11 months) or placebo (9 patients, for a mean of 7.7 months). Sixteen patients treated with chlortetracycline showed reductions in frequency and severity of infection compared to only two patients in the placebo group.

The MRC trial (1957), remains one of the most informative studies reporting the effects of long-term antibiotic treatment. One hundred and
twenty-two patients were randomised to receive penicillin (38 patients), oxytetracycline (44 patients), or placebo (40 patients) over 1 year. Three patients died, one in each group, four patients defaulted (two oxytetracycline, two placebo), one patient was excluded following the diagnosis of cystic fibrosis (CF), and two patients failed to tolerate the study medication. The final analysis was therefore based on 112 patients. Interestingly, none of the data were subjected to statistical analysis. Within 2 weeks, the 24 h sputum volume in the oxytetracycline group was reduced to 55% of pre-treatment volume and the purulent fraction was reduced by 50%. These changes were sustained throughout the trial. For the penicillin and placebo groups, the 24 h sputum volume was reduced to 70% and 80%, respectively. During the year on treatment there were definite advantages for patients treated with oxytetracycline with respect to days off work and confinement to bed. All groups showed improvements for cough, haemoptysis and dyspnoea.

Cherniak et al. reported a trial evaluating tetracycline, oleandomycin/penicillin combined, penicillin alone and placebo over 3–22 months.26 Not all the patients had bronchiectasis (45 of 67 subjects). The groups differed in terms of disease severity with discrepancy between 24 h sputum volumes and chronic expectoration of either mucoid or purulent sputum. The tetracycline group suffered significantly less acute lower respiratory tract infections and fewer days with fever than the placebo group. Otherwise, there were no significant differences between groups. The heterogeneity of the patients enrolled makes interpretation of this trial difficult.

The trial reported by Currie et al. in 1990 studied 38 patients over 32 weeks27 and was designed to test the vicious cycle hypothesis using high-dose long-term treatment. Nineteen subjects were randomised to receive Amoxyl sachets 3 g b.i.d. or matched placebo. There were nine drop-outs (four amoxycillin, five placebo) two of these within the first 2 weeks and therefore their data were not analysed. The withdrawals were due to failure to respond (five subjects), adverse events (three subjects) and non-compliance (one subject). Data from 36 patients were analysed and the primary end point of the study was objective response assessed by changes in 24 h sputum volume, sputum culture results, or FEV1. A significantly higher proportion of the amoxycillin-treated patients responded compared to the placebo group (11/17 and 4/19, respectively). The number of exacerbations between the groups was not different although there was a reduction in the severity of exacerbations in the amoxycillin-treated patients. The 24 h sputum volume was reduced to 20% of pre-treatment levels for the amoxycillin group compared to 80% of pre-treatment volume for the placebo group. Whilst there was a reduction in H. influenzae cultured from the sputum in the actively treated patients, those individuals who continued to culture this bacteria showed a tendency towards increasing resistance. There were 21 patients who cultured P. aeruginosa (13 amoxycillin, eight placebo). There were no differences between the groups for adverse events.

The experience of 10 patients who had taken ciprofloxacin for a mean period of 412 ± 273 days (range 90–860) was reported by Rayner et al.28 The dose varied between 500 and 1500 mg taken in divided doses, two or three times a day. Nine patients had positive sputum cultures at the beginning of treatment (five P. aeruginosa, all sensitive to ciprofloxacin, three H. influenzae, and one Streptococcus pneumoniae). Following treatment, six patients showed no growth, two of whom had been colonised with P. aeruginosa. One patient grew S. pneumoniae instead of P. aeruginosa and two continued to yield P. aeruginosa which had become resistant to ciprofloxacin. The development of resistance to ciprofloxacin by P. aeruginosa was associated with clinical deterioration. Seven patients reported improvements in their condition on treatment and there were significant reductions in exacerbations and hospital admissions. There were also significant improvements in peak flow and residual volume on lung function testing. There were no adverse events and the therapy was considered to be safe. The authors comment that ciprofloxacin, whilst concentrated in bronchial mucosa is only bacteriostatic against S. pneumoniae and therefore not likely to effect eradication of this organism in patients showing this bacteria on sputum culture.

A further trial evaluating the use of quinolones in the prophylaxis of exacerbations of chronic respiratory tract infections was published by Watanabe et al.29 Fifty-eight patients, inclusive of only 19 bronchiectatics were studied for 6 months. The remaining patients’ diagnoses included emphysema, chronic bronchitis, previous tuberculosis, and diffuse panbronchiolitis. All of the individuals for this trial were selected on the basis that their chronic illness was characterised by recurrent infection. Exacerbations in the 6 months prior to study entry was a prerequisite for inclusion. The patients were randomised to receive either ofloxacin 200 mg o.d. (regimen one) or ofloxacin 200 mg t.i.d. taken for 2 weeks at a time every fortnight (regimen two). The corrected mean exacerbation
rate per 6 months was reduced from pre-study 2.47 to intra-study 0.59 for regimen one and from pre-study 2.66 to intra-study 0.95 for regimen two. The drugs were well tolerated and only one P. aeruginosa isolate (out of 12 patients showing this organism) developed resistance to ofloxacin but without clinical deterioration. The authors concluded that both regimes were effective at reducing exacerbations, but found no statistical difference between them. They favoured the use of ofloxacin 200 mg daily.

The same group published a further study comparing ciprofloxacin, erythromycin, or a combination of the 2 over 6 months. Not all the patients had a diagnosis of bronchiectasis (19 out of 50) although six patients were diagnosed with diffuse panbronchiolitis. As previously, all the patients suffered from recurrent lower respiratory tract infection. The results showed significant protection against exacerbations in the patients randomised to receive ciprofloxacin or the combination of ciprofloxacin and erythromycin. There were no significant adverse events and only one P. aeruginosa isolate developed resistance to ciprofloxacin.

The data reported by Koh et al. were derived from a group of 25 children randomised to receive roxithromycin (4 mg/kg) or placebo over 3 months. All of the children had proven bronchiectasis and heightened airways responsiveness to methacholine (PC20 < 2.5 mg/ml). The study was based on the unproven premise that bronchial hyperreactivity was a feature of bronchiectasis and that this played a part in the pathogenesis of the condition by inhibiting respiratory clearance mechanisms. Following treatment, the patients randomised to roxithromycin had a significant reduction in sputum purulence, leucocyte scores and airways responsiveness to methacholine. No changes were seen in the placebo group. The paper does not state whether the subjects had chronic expectoration of purulent sputum and seven of the children had co-existing asthma.

Tsang et al. studied 37 chronic stable bronchiectatic patients to evaluate the benefits of low-dose erythromycin treatment for 2 months. Ten of the erythromycin patients and six of the placebo patients showed positive sputum cultures for P. aeruginosa. The primary outcomes, sputum volume and lung function (FEV1), were significantly improved on erythromycin compared with placebo. No changes were seen for sputum pathogens, leucocytes or leukotrienes. Neutrophil elastase was not measured.

There are a number of trials showing the benefits of inhaled antibiotics in the management of CF patients. Orriels et al. randomised 17 patients with non-CF bronchiectasis, all of whom were colonised with P. aeruginosa, to receive inhaled ceftazidime 1 g b.i.d. and tobramycin 100 mg b.i.d. or standard management alone. The trial duration was 1 year and all patients received a 2-week course of intravenous antibiotics prior to embarking on the study period. There were significant benefits in favour of the inhaled strategy for both numbers of admissions and in-patient days. There were no differences for lung function between the two groups, which showed a progressive decline, nor any differences for resistance patterns for P. aeruginosa.

A second clinical trial looking at the use of inhaled antibiotics in bronchiectasis was reported by Barker et al. Seventy-four patients with bronchiectasis and chronic infection with P. aeruginosa were randomised to receive tobramycin 300 mg b.i.d. or matched placebo over 4 weeks. The primary end point was a reduction in P. aeruginosa density on sputum culture (expressed as log10 colony forming units/g sputum). The study showed significant reductions of microbial density on sputum culture and the organism was eradicated in 35% of actively treated patients 2 weeks after discontinuing the treatment phase (i.e. at 6 weeks). No eradication of P. aeruginosa was seen in the placebo group. The authors reported objective improvement in 62% of the tobramycin patients and 38% of the placebo patients. In contrast, the subjective assessments indicated a non-significant trend for increase in cough, wheeze and dyspnoea for the tobramycin group. There were no differences for resistance patterns between treatments not for FEV1.

A recent systematic review has drawn together this evidence and included the randomised controlled trials. Where possible the data have been synthesised to undertake meta-analysis. Only six trials fulfilled the criteria for inclusion and therefore a number of the aforementioned studies, despite contributing to the evidence base, can only be discussed in isolation and have not been a part of summary statistics for treatment effects. The review included a total of 302 patients, 40% of which were derived from one study. The antibiotic duration varied from 4 weeks to 1 year. There were 40 withdrawals due to adverse events or intolerable side effects. Due to the diversity of the trials, it was only possible to do limited meta-analysis. Response rates during the course of treatment showed significant effects in favour of active intervention, Peto odds ratio 0.3, 95% confidence interval, 0.14, 0.63, although for exacerbation rates there were no differences in...
favour of antibiotics. Outcome measures looking at withdrawals and lung function showed no differences between interventions and placebo.

Summary

To arrive at a consensus on the issue of long-term antibiotic treatment in the management of bronchiectasis is not easy given the diversity of the condition in terms of aetiology, severity, and in particular, microbial culture results. This article has made no attempt to consider the issue of aetiology in the context of long-term antibiotic treatment as insufficient data are available. Furthermore, the evidence that does exist represents extreme variety in terms of study design, end points (sputum markers, symptoms, lung function), duration (ranging from a few weeks to 1 year), subject selection (children/adults), antibiotic selection (arbitrary/specific), microbiology (exclusively Pseudomonas colonisation or otherwise), and drug delivery (oral/parenteral/nebulised).

The issue of P. aeruginosa colonisation is worthy of special attention. Pseudomonas colonisation is associated with a worse prognosis in bronchiectasis as demonstrated by physiological and radiographic studies. Whilst most of the trials evaluating patients with mixed sputum culture results (i.e. not P. aeruginosa), have shown that in vitro testing does not predict clinical outcomes, individuals colonised with P. aeruginosa do require tailored antibiotic regimes. Only two trials specifically addressed the issue of P. aeruginosa and these studies adopted inhaled regimes. The authors of the oral quinolone studies did not confine themselves to patients colonised by P. aeruginosa (nor exclusively bronchiectatic patients in two trials) and further research looking at oral regimes against this bacteria remains to be reported. On the basis of the evidence reported, nebulised antibiotics appear to be effective anti-pseudomonal treatment in both CF and non-CF bronchiectasis.

The use of macrolide antibiotics in a number of studies is of interest. It is possible that these drugs may exert benefits through non-antibacterial mechanisms. Diffuse pan-bronchiolitis has been recognised as a progressive condition characterised by sputum production, rhinosinusitis, and chronic P. aeruginosa colonisation. Erythromycin has been shown to be effective treatment for this condition despite the Pseudomonas colonisation and this is supported by pre-clinical data suggesting non-antibacterial properties of macrolides possibly targeted against inflammatory effects of P. aeruginosa. Therefore, the studies reporting macrolides should be interpreted with this issue in mind.

The systematic review of six randomised controlled trials warrants brief discussion. Notwithstanding the limited meta-analyses and the issues of diversity already discussed, the results support a marginal advantage in the use of long-term antibiotic treatment. However, it is noteworthy that three of the included studies did not state a primary end point nor give details of power calculations which raises the doubt about type II statistical errors for negative analyses. This is particularly relevant to measures of lung function which were negative in all the review trials with the exception of the study reported by Tsang. Given the data showing the effects of antibiotic treatment on neutrophil elastase and sputum/serum albumin concentrations, it is disappointing that the review trials did not specify the patients who had chronic expectoration of purulent sputum. Furthermore, many of the other clinical trials also failed to make this observation and therefore correlation of clinical responses and possible mechanisms for these patients is lacking.

Overall, the trials cautiously support the benefits of long-term antibiotic treatment although these advantages are only maintained during treatment and no enduring benefits have been reported. There is a body of evidence that suggests that this intervention does reduce ongoing airways inflammation and therefore might be expected to influence the natural history of the disease. It would appear that any advantage will be relevant to those patients who expectorate purulent sputum. For individuals colonised with Pseudomonas, specific antibiotic regimes should be selected and there may be a role for long-term nebulised treatment. For patients not colonised with P. aeruginosa, in vitro sensitivity testing does not predict clinical responses. Furthermore, the emergence of antibiotic resistance does not appear to be a major issue for these patients. As a rule the treatments are well tolerated. Further, carefully designed and focused research is required to take this clinical challenge forward. In a disease of diminishing prevalence, the difficulties of designing adequately powered trials and recruiting sufficient numbers of patients are daunting. Furthermore, in a condition of such differing aetiologies, it should be anticipated that there might be an even greater heterogeneity in clinical responses to treatment. There is still considerable debate as to the optimal outcome measures and we have yet to learn how best to identify with certainty those patients who are likely to progress to severe disability.
and who are most likely to benefit from targeted interventions.

Practice points

- There is some evidence that long-term antibiotics have a role in the management of patients with chronic sputum purulence.
- The treatment is well tolerated and emerging resistance does not occur in most patients.
- In patients not already colonised with *P. aeruginosa*, in vitro sensitivities may not predict clinical outcomes.
- *P. aeruginosa* requires specific antibiotic regimes.
- Nebulised treatment has a role in management.
- Macrolides may work through non-antibacterial mechanisms.

References


