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New Therapies for the prevention and treatment of exacerbations of bronchiectasis

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Abstract

Purpose of the review: Exacerbations of bronchiectasis have a major impact on quality of life, healthcare costs and long term risk of complications. Preventing exacerbations is one of the major goals of treatment. Bronchiectasis is increasingly recognised and the impact of bronchiectasis exacerbations on daily clinical practice is also increasing.

Recent findings: Preventing bronchiectasis exacerbations is dependent on appropriate risk assessment, identifying the patients at highest risk in order to rationally target preventative therapies. Inhaled and oral antibiotic treatments can target chronic bacterial infection which is one of the major risk factors for exacerbation. Although the data is weak, airway clearance is an important part of long term management including in patients with frequent exacerbations. Anti-inflammatory therapies such as inhaled corticosteroids do not currently have a major role outside co-morbid COPD and asthma, but further studies are required.

Summary: Treatment of acute exacerbations involves prompt administration of antibiotic therapy with usually 14 days of oral, or for severe exacerbations, intravenous antibiotics. The role of corticosteroids is not established and there is little data on the optimal management approach for acute exacerbations. Home intravenous therapy can reduce healthcare costs and improve patient satisfaction with care. A number of large randomized controlled trials are currently enrolling or have recently completed raising the possibility that the treatment paradigm may change in the near future.

Introduction

Bronchiectasis is increasing in prevalence worldwide with most recent data from Spain indicating a rate of 362 per 100,000 to add to data from the UK indicating rates of 486 per 100,000 in men and 566 per year in women.(1,2) Hospitalisations are increasing year on year in the UK, Germany, New Zealand and in other countries.(3,4) Navaratnam also demonstrated an increase in admissions to ICU for exacerbations of bronchiectasis of 8% per year in the UK.(5)

Bronchiectasis is a term used both to refer to a radiological appearance, defined as abnormal and usually permanent dilation of the bronchi, but when used to describe a disease should be defined by the presence of the radiological appearance plus a clinical syndrome consisting of cough, sputum production and recurrent respiratory tract infections.(6,7) The combination is sometimes referred to as clinically significant bronchiectasis. (8)

Bronchiectasis is a common finding in patients with chronic respiratory diseases such as COPD and asthma.(9-11) The significance of bronchiectasis in these patient groups is not fully understood and may represent a consequence of the inflammation in these disorders, a misdiagnosis (where a patient with a primary process leading to bronchiectasis is misdiagnosed with COPD or asthma), or a co-morbidity where two different processes co-exist in the same patient.(9) The situation is complicated by the fact that bronchiectasis is usually defined by the bronchial-arterial ratio (B-A ratio). At any level on CT, the bronchial diameter should be less than the adjacent vessel.(12-14) A ratio >1 is usually taken to indicate bronchiectasis. In independent investigations Tan et al, has shown that bronchiectasis was present in 19.9% of normal never smoking controls without respiratory symptoms, 19.9% of smokers, 14.1% of patients with mild COPD, 22% of patients with moderate COPD and 35.1% of patients with severe or very severe COPD.(14) This indicates that our definition of bronchiectasis may be too sensitive as a mild increase in the B-A ratio is observed in 20% of healthy controls, and therefore the true rate of pathological dilatation may be exaggerated.(14)

Dias et al recently demonstrated that in the majority of cases of increased B-A ratio in COPD patients, the change in the ratio was due to a reduced size of the blood vessel. These patients therefore do not strictly have bronchiectasis, since the name requires dilation of the bronchi.(15)

These data are presented here to remind the reader that the following recommendations and data refer to clinically significant bronchiectasis only, and should not be applied to the broad range of individuals with an abnormal B-A ratio without the corresponding clinical features.

Exacerbations of bronchiectasis

Even within the definition of clinically significant bronchiectasis, the disease is highly heterogeneous in terms of causes, impact and outcomes.(16-19) Up to 60% of cases are idiopathic, with post-infection being recorded as the most frequent underlying “cause”. Less frequent causes such as allergic bronchopulmonary aspergillosis, connective tissue disease, non-tuberculous mycobacterial disease and immunodeficiency must be identified and treated as they usually require a specific treatment not described below.(20-23) Once the initial identification and treatment of underlying causes has been performed, the disease still presents individual “phenotypes”.(24)

Exacerbations of bronchiectasis typically presenting with a combination of increasing cough, sputum production, increasing sputum purulence, malaise, fever or worsening breathlessness. There is no universally accepted definition to date and an exacerbation can be highly different between individuals.

What causes exacerbation is uncertain. Viruses have been identified frequently in bronchiectasis.

Gao et al studied bronchiectasis exacerbations and found 49% of patients had viruses in nasopharyngeal swab or sputum at exacerbation compared to 18.9% of patients when stable.(25)

Bacteria are frequently isolated at exacerbation, but are also seen in sputum cultures from 70% of patients when clinically stable.(26-28) It is not known the extent to which increases in bacterial load,

changes in bacterial strain or changes in the composition of the airway microbiome might explain the development of exacerbations of bronchiectasis. Tunney et al studied the airway microbiome using 16s rRNA sequencing to obtain a global view of the microorganisms in sputum in stable bronchiectasis and exacerbations and show relatively little change at exacerbation, with a trend towards a decrease in microbial diversity.(29) The role of fungi is unknown.

Clinical predictors of exacerbation have been defined. We developed a clinical prediction rule for bronchiectasis, the bronchiectasis severity index (BSI) which identifies patients at higher risk of mortality, severe exacerbations, outpatient exacerbations and worse quality of life.(30-32) In a multivariable analysis of the predictors of severe exacerbations the strongest predictors were a prior history of severe exacerbations (HR 13.5 95% CI 9.40-19.5), FEV1 <30% predicted (HR 1.52 95% CI 1.03-2.25), MRC dyspnoea score >3 (HR 2.4 95% CI 1.7-3.5), *Pseudomonas aeruginosa* colonisation (HR 2.2 95% CI 1.4-3.4), infection with other organisms (HR 1.7 95% CI 1.1-2.4) and greater radiological extent of disease (HR 1.5 95% CI 1.0-2.2). (30) Therefore more extensive disease, determined by radiology or lung function, and chronic infection with bacteria are the primary predictors of frequent exacerbations. Since chronic infection is the major modifiable risk factor, since explains why a priority in clinical management is to suppress or eradicate chronic infection.(33)

P. aeruginosa is a key pathogen, being present in 10-40% of patients depending on the population studied.(30-33) It is well known as a determinant of poor outcome in cystic fibrosis and the eradication or suppression of *P. aeruginosa* is a standard of care in CF.(34-37) In bronchiectasis, predominantly European data shows that chronic infection with *P. aeruginosa* increases the risk of death by 3-fold, increases the risk of hospital admission by 7-fold and is also associated with worse lung function and a worse quality of life. (38)

Bacteria drive neutrophilic inflammation, with higher bacterial loads being associated with more inflammation and also being associated with a higher frequency of exacerbations.(38) A recent prospective study of 381 patients examined the key neutrophil biomarker neutrophil elastase and

found a clear association between elastase activity and both time to the next exacerbation and frequency of exacerbations.(39) The linked biomarker desmosine was independently associated with an increased risk of severe exacerbations.(39) It is not known the extent to which other types of airway inflammation such as eosinophilic inflammation, impact on bronchiectasis exacerbations, but there is clearly a population without neutrophilic disease that still have frequent exacerbations.

Co-morbidities are also important in both disease severity and the risk of exacerbations.(40,41) A recent prospective study from the EMBARC network across Europe showed that in 986 patients the strongest predictor of 5-year mortality was having multiple co-morbidities and that patients with greater high risk co-morbidities (using a newly developed and validated bronchiectasis aetiology and co-morbidity index- BACI) also had a higher frequency of exacerbations.(40) Whether this is mediated by increased systemic and airway inflammation associated with co-morbidities or whether this is due to some exacerbations being due directly to decompensated co-morbidities such as heart failure and cardiovascular disease is unclear. Bronchiectasis appears to increase the risk of cardiovascular disease and cardiovascular complications.(41)

Figure 1 shows some of the known influences on exacerbation susceptibility

Brill et al have provided the most detailed study of the impact and symptom burden at exacerbation. In 32 BE patients completing diary cards, patients had an average of 4 days of symptoms prior to treatment and the average duration of symptoms was 16 days.(42) 16% did not recovery by day 35 indicating a significant number of patients that experience a prolonged “exacerbation recovery” period where health status is significantly worse than prior to the exacerbation.(42) There is relatively little data on how to enhance recovery and preserve health status post-exacerbation.

Prevention of exacerbations

Figure 1 provides a useful framework for the treatment of exacerbations. Bacterial infection is targeted with prolonged antibiotics. Co-morbidities such as cardiovascular disease or underlying

causes such as ABPA should be treated. Airway clearance should be optimised and patients should be vaccinated against influenza virus.

Antibiotic therapies

Controlling chronic bacterial infection reduces inflammation and there is increasing evidence that prolonged antibiotic treatment can improve clinical outcomes.(38)

Inhaled antibiotics are widely used in cystic fibrosis bronchiectasis but none are licensed for use in bronchiectasis excluding CF.(43) The most widely used agents are colistin, gentamicin and tobramycin in Europe.(44) Colistin has been tested in a 6 month randomized controlled trial by Haworth et al. The trial enrolled 144 patients randomized to colistin or placebo. Median time to exacerbation was 111 days in the placebo group and 165 days in the active group, which narrowly missed statistical significance ($p=0.1$). (45) The i-Neb device allows monitoring of compliance the result was statistically significant in the compliant population. There was also a marked improvement in quality of life using the St.Georges Respiratory Questionnaire (SGRQ).(45)

Tobramycin has been tested in a number of small randomized trials with mixed results. Although some clinical benefits have been noted, a high rate of bronchospasm has also been observed which is a potential problem with all inhaled antibiotics.(46)

Brodt performed a meta-analysis of all available inhaled antibiotic trials and reported a significant reduction in exacerbation risk (RR 0.72 95% CI 0.55-0.94), while also noting a small increase in antibiotic resistance and a rate of bronchospasm of 10%.(47)

While this estimate is useful, the appropriateness of pooling all available data should be questioned. Results have been highly variable between different inhaled antibiotic drugs, with no benefit in terms of exacerbations with aztreonam, for example, when tested against placebo in a population of patients with Gram-negative airway infection.(48) Therefore the data for each individual drug should

be considered both in terms of safety and efficacy before choosing the optimal treatment for the patient.

Most patients receiving inhaled antibiotics in real-life clinical practice have a history of *P. aeruginosa* infection and have a history of frequent exacerbations.(44)

Long term oral antibiotic treatment has advantages in terms of convenience and compliance compared to inhaled antibiotics but also carries increased risks of systemic side effects and antibiotic resistance.(49-51) The most intensively studied are the macrolides, although it remains a subject of debate as to whether these function primarily as an antibiotic or an anti-inflammatory agent. 3 randomized controlled trials of 6-12 months treatment in bronchiectasis patients with a history of exacerbations have unequivocally shown a reduction in the frequency of exacerbations.(49-51) Up to 20% of patients experience gastrointestinal side effects with azithromycin or erythromycin, and there are reports of hearing loss and prolongation of the QT interval. Patients should be carefully screened for NTM infection to avoid the potential consequences of macrolide resistance NTM.

Tetracyclines and penicillins have also been tested in historical studies and are occasionally used at low doses as prophylactic therapy, for example in patients with *H. influenzae* infection. The data to support this is limited.(52-54)

Patients who continue to exacerbate despite an inhaled antibiotic may benefit from combined treatment with an oral and inhaled antibiotic. Notably, macrolides inhibit *P. aeruginosa* virulence factors and may also have some antimicrobial effect and so combined treatment may be beneficial in patients with *P. aeruginosa* infection.(55,56)

Similarly, patients who continue to exacerbate despite macrolide therapy may benefit from an alternative oral antibiotic or a trial of an inhaled antibiotic.

Patients who have failed to respond to trials of prolonged antibiotic treatment, either because of poor tolerance or lack of efficacy may benefit from 6-8 week intravenous antibiotic treatments.(57)

A schematic of antimicrobial treatment is shown in figure 2.

P. aeruginosa eradication treatment with oral ciprofloxacin for 2 weeks or intravenous antipseudomonal antibiotics plus inhaled antibiotics is standard of care on the first isolation of *P. aeruginosa* in CF patients and it is the authors practice as well as guideline recommendations to attempt eradication on first isolation in patients with bronchiectasis.(58)

Anti-inflammatory therapies

Inhaled corticosteroids are the most frequently used therapy for patients with bronchiectasis despite an absence of high quality randomized controlled trial evidence.(59) A Cochrane review found no clear patient benefit from the small trials that have been conducted and side effects include a possible increase risk of pneumonia as has been observed in COPD.(60-62) Inhaled corticosteroids should be reserved for patients with bronchiectasis and COPD, or those with asthma.(63)

Vaccination

Patients with bronchiectasis should receive influenza vaccination, since they are at higher risk of influenza complications and influenza can be associated with exacerbations. Guidelines also recommend that patients with bronchiectasis should receive pneumococcal vaccination.

Chest clearance and mucoactive drugs

All patients with bronchiectasis should be trained to perform airway clearance.(64) Mucoactive drugs may be helpful in patients expectorating large volumes of sputum and with exacerbations despite adequate airway clearance techniques. Options include isotonic or hypertonic saline, carbocisteine and inhaled dry powder mannitol.(65-67) Two randomized trials of mannitol failed to achieve their primary end-point.(66,67) A comparison between isotonic and hypertonic saline in found no differences in terms of exacerbations or quality of life.(65) Larger studies are planned.

Treatment of exacerbations

There are very few studies of the treatment of acute exacerbations of bronchiectasis.(54)

Exacerbations are classified into those requiring antibiotic treatment, and those severe exacerbations requiring admission to hospital and intravenous antibiotic treatment. 14-days of antibiotics are recommended with high doses given the high bacterial loads associated with bronchiectasis, although such recommendations may change in the future as data emerges.(54)

Intravenous antibiotics are indicated for patients with respiratory failure, sepsis, inability to take oral therapy or for patients who have failed to respond to an adequate oral course of therapy or who isolate a pathogen resistant to all available oral drugs.(54)

Exacerbations due to *P. aeruginosa* can be treated with high dose oral ciprofloxacin if mild, for 14 days. If admitted to hospital, there is no evidence that combination antibiotic treatments are superior to monotherapy with an effective anti-pseudomonal antibiotic.(54) The authors practice is to use monotherapy for older patients at higher risk of adverse effects, particularly from aminoglycosides (68), while using combination treatments for patients with drug resistance *P. aeruginosa* to attempt to limit the further development of resistance. Adjunctive inhaled antibiotics have been attempted with limited benefit.(69)

Oral corticosteroids are not indicated for bronchiectasis exacerbations, unless COPD or asthma are present.

Patients should intensify chest clearance techniques during an exacerbation and a review by a specialist physiotherapist during hospitalisation is valuable. Hydration with intravenous fluids may also aid airway clearance during inpatient admissions.

Future directions

Two large randomized controlled trials of inhaled antibiotics will report in 2017 and may change the treatment paradigm for bronchiectasis.(70,71) Alternatives to antibiotics are urgently needed and De Soyza recently reported the results of a novel anti-inflammatory, the CXCR2 antagonist AZD5069 in bronchiectasis. The study showed a reduction in the primary outcome of sputum neutrophil count (by 69%) without a reduction in exacerbations, for which the study was not powered.(72) There was an increase in adverse effects including pneumonia suggesting that reducing neutrophil counts may be harmful in some patients with bronchiectasis.(72) Further development of anti-inflammatory therapies that modulate neutrophil function rather than reducing neutrophil numbers may have greater success.

A recent statement from the European Bronchiectasis Network (EMBARC) has listed key research priorities in the field including a number relating to exacerbations.(73) Large multicentre networks such as EMBARC and the US bronchiectasis registry have the potential to generate data that will answer some of the outstanding questions above regarding bronchiectasis exacerbations, as there are a limited number of bronchiectasis RCTs.(74.75) The first results of the US Registry have recently been published with 1826 patients enrolled from 2008-2014. 79% of patients were female and 63% had a history of NTM isolation of NTM disease. *P. aeruginosa* was the most frequently isolated

bacterial pathogen. (74) Longitudinal data to compare treatment outcomes and identify best practice will be the most informative and are awaited.

Conclusion

Bronchiectasis exacerbations are common, with an important healthcare burden. Treatment pathways for acute exacerbations are poorly defined but there are now a number of therapies with evidence to support a role in prevention of exacerbations. Ongoing registries and randomized trials are likely to provide future guidelines with a stronger evidence based approach to the disease.

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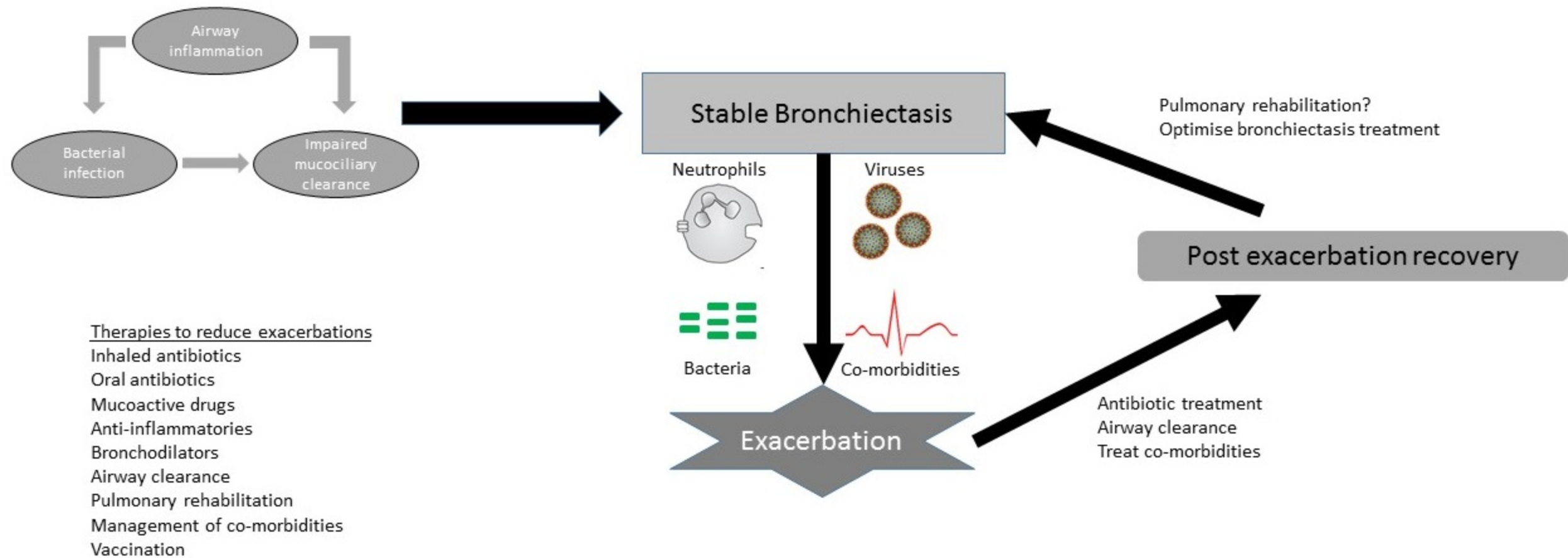
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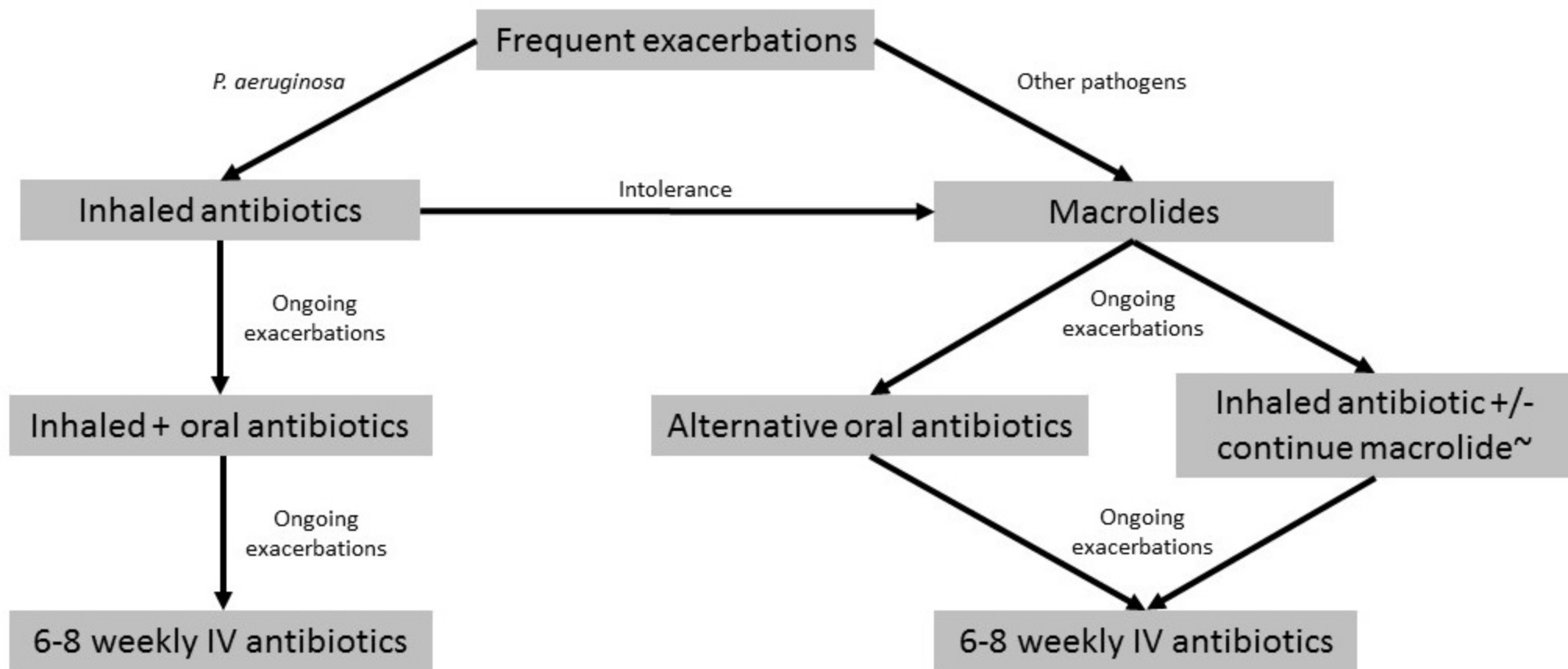
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Figure 1. The vicious cycle of bronchiectasis and the drivers of exacerbation.

Figure 2. A model protocol for the use of inhaled and oral antibiotic treatment for patients with frequent exacerbations of bronchiectasis.





At each stage

- Optimise airway clearance and non-antibiotic treatment
- Exclude causes of frequent exacerbations other than airway infection
- Take into account risk:benefit ratio, adherence and antibiotic resistance