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Key points

- Postural drainage, active cycle of breathing techniques and pulmonary rehabilitation are non-pharmacological treatment options that should be offered to all patients with non-cystic fibrosis bronchiectasis (NCFB).
- Eradication of *Pseudomonas aeruginosa* (PA) colonisation in patients without an acute exacerbation remains debatable.
- Sputum cultures are the leading and most readily available tool to detect patients with chronic colonisation by PA and should be performed in all patients with NCFB.
- Antibacterial monoclonal antibodies and vaccine studies have shown promising results in the prevention of chronic colonisation with PA and should stimulate new studies in NCFB.
- NCFB patients colonised with PA are at more risk of a rapid decline in lung function, worsening quality of life and more hospital admissions.
- Dual therapy is a promising option for the management of patients with PA-related exacerbations.
- Patients with PA-related exacerbations benefit from prolonged courses of antibiotics (*i.e.* 14 days) but emerging and future studies, including dual therapy, may show promising results with shorter courses.
- Endophenotyping bronchiectasis to address its inherent heterogeneity is a promising avenue for future investment and research.

Review

Hot topics and current controversies in non-cystic fibrosis bronchiectasis

Non-cystic fibrosis bronchiectasis (NCFB) is a neglected and orphan disease with poor advances through the 20th century. However, its prevalence is rising and with this come new challenges for physicians. Few guidelines are available to guide clinicians on how to diagnose and manage patients with NCFB. Many areas of debate persist, and there is lack of consensus about research priorities most needed to advance patient care and improve clinical outcomes. In this review, we highlight the current hot topics in NCFB and present updated evidence to inform the critical areas of controversy.

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Non-cystic fibrosis bronchiectasis (NCFB) is a chronic lung disease characterised by permanently damaged airways, which has gained international attention because of its increasing prevalence, the economic burden to healthcare systems and associated morbidity and mortality [1–4]. It is a heterogeneous entity and previously thought to be rare, resulting in the terminology “orphan disease” [5], with the little advance made over the 20th century. NCFB has, however, received increasing focus over the past two decades, with proposed new therapies, perspectives and even endophenotypes now considered when studying and treating NCFB patients [6–9].

The incidence of NCFB is 2–5 patients per 1000 population and tends to be more frequent in the elderly [6, 10]. The aetiology of NCFB is multifactorial, but the majority of patients remain idiopathic [11]. Unfortunately, no curative treatment or medications specifically approved to treat NCFB patients currently exist [3, 12–14]. NCFB

has a progressive course primarily determined by the rate of exacerbations, the majority of which are related to *Pseudomonas aeruginosa* (PA) [15, 16]. Consequently, research efforts directed to prevent colonisation by PA and to treat its associated acute exacerbations remain a clinical priority.

As in many areas of medicine, precision medicine has emerged as a promising strategy to improve clinical outcomes in patients with NCFB; thus, endophenotypes are being evaluated to identify common characteristics that may be tailored for specific treatments and interventions in individual patients [14, 17, 18]. Therefore, it is now accepted that a single treatment approach is not appropriate for all NCFB patients. In addition, in 2017, the European Respiratory Society guidelines for the diagnosis and management of adult patients with NCFB were published [6], but as the authors of this guideline and other experts highlight, many areas of uncertainty exist [1, 6, 16, 19–24]. In light of this, we will highlight in this review some current

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Non-cystic fibrosis bronchiectasis (NCFB) is a neglected and orphan disease with poor advances through the 20th century. Physicians should understand available data to provide evidence-based treatments to patients suffering from NCFB. <http://bit.ly/2kBGVsx>



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clinical hot topics in NCFB and discuss the state of the current evidence in these areas.

What are the most effective non-pharmacological treatment options for mucus clearance in bronchiectasis?

Non-pharmacological mucus clearance (or airway clearance techniques (ACTs)), within the margins of cystic fibrosis bronchiectasis or NCFB patients, represents a vital component of treatment, permitting a noninvasive, low-risk strategy to decrease acute complications [6, 18, 19]. The existing ACTs are plentiful; however, in this section, we will explore some of the options that have demonstrated usefulness in the eradication of mucinous obstruction of the airway in patients with NCFB.

Postural drainage is a technique that has been shown to be an effective airway clearing modality, more so than other more invasive strategies [25]. Postural drainage is achieved by placing the patient horizontally with the head at a lower angle than that of the thorax (approximately 30°), with possible accompanied head tilting, to induce mucus migration from the peripheral bronchial airway to expectoration. This technique is effective, albeit uncomfortable for the patient, which might suggest low adherence.

Among the better-known ACTs are manual techniques involving some form of percussion or rhythmic vibration applied to the chest wall to increase dislodging and production of sputum. Evidence suggests that manual ACTs in combination with postural drainage yield a better result for mucus clearance [26]. Percussion and vibration techniques, however, require a caregiver, are uncomfortable for patients and may increase gastro-oesophageal reflux or nausea.

In contrast, the patient can easily perform the active cycle of breathing technique (ACBT), as this does not require a caregiver or any other tool. The process implies a three-step progression initiated by a series of cycles starting with controlled breathing (low end-tidal pressure exercises), followed by thoracic expansion exercises (slow deep inspiratory movements through the nose in order to control flow and temperature) and finally forced expiration techniques (implying increase in turbulent flow by acceleration through an open upper airway). There are currently insufficient data, including data for NCFB, to consider ACBT as most superior among the described ACTs; nonetheless, this therapy seems to be comparable and straightforward and is a consideration for clinicians [27]. Furthermore, ACBT carries little risk for the patient and is easily taught. A systematic review analysed different sputum clearance techniques, none of which involved the complete ACBT process [28]; however,

it did reveal forced expiration techniques as a valid method of airway clearing, mainly when supported by pharmacological therapy [3, 29].

Positive expiratory pressure (PEP) is one of the most effective ACTs and involves a device with a one-way valve, creating an unrestricted effort during inspiration. The patient proceeds to breathe against positive pressure exerted by the device and, through this, maintains an open airway, therefore increasing clearance [29–32]. Nevertheless, there is little evidence to suggest its superiority to other ACTs. There are multiple other uses of PEP associated with various types of valves and pressures that have shown varied results, including (at best) equivalency to other ACTs [31, 32]. PEP may also not be readily available at most healthcare centres; however, several prior studies do suggest clear benefits to general sputum discharge and quality of life [33].

Finally, exercise and rehabilitation approaches are accompanied by the best evidence concerning mucus clearance and lung function [34]. The mechanisms through which exercise provides an improvement are still yet to be fully understood, but it is hypothesised that an increased ventilatory demand creates a combination of factors that maintain a constant tidal pressure accompanied by a flow of mucus towards the upper airways. Evidence suggests that exercise (in addition to PEP or other ACTs) reduces mucous viscosity and further increases lung capacity reserves by maintaining open peripheral airways [29–32].

Pulmonary rehabilitation covers a wide variety of tools provided to patients, including (but not limited to) education, exercise, social and psychological support, and nutritional evaluation. These are low-risk interventions that carry benefits towards improving symptoms and generally better quality of life [35]. The broader term of ACTs does not currently cover exercise itself; nevertheless, exercise belongs in the higher spectrum of non-pharmacological treatments for cystic fibrosis and NCFB and should be considered and prescribed.

In summary, all the above ACTs are proposed to have benefit. However, with limited available data comparing them, it is essential to promote new studies to improve the evidence-based support. ACTs remain a critical clinical topic for treatment and retain relevancy for NCFB.

Should we pursue the eradication of PA colonisation in patients without an acute exacerbation?

To this day, PA poses a key risk in the prognosis of NCFB. Despite this, no clear indicator for risk-factor-based treatment is offered, given its broad resistance spectrum and ability to develop resistance rapidly. Early diagnosis and screening for PA have proven to be useful in the prevention of

bronchial infection [1, 5, 18]. Colonised patients, in general, demonstrate rapid decline in lung function, worsening of symptoms and quality of life, and more hospital admissions [36, 37]. Consequently, the pursuit of eradication appears a viable option for the prevention of infection, improvement of quality of life, and better clinical outcomes.

A 2015 study by ORRIOLS *et al.* [38] raises similar questions to those posed here. By following a cohort of 35 patients over 15 months, employing intravenous and nebulised tobramycin to 16 patients, the authors showed benefit, although some treatment arm patients were withdrawn due to bronchospasm. The number of exacerbations and days of hospitalisation were significantly reduced in patients that tolerated tobramycin *versus* placebo. During this study, no evidence of resistant PA strains was detected; however, other opportunistic organisms were identified in sputum culture. As a point of discussion, PA seems to be associated more strongly with patients with severe disease. The PA growth ecosystem seems to necessitate an advanced disease stage to flourish, implying a more significant mucus burden, therefore reducing the calculated effectiveness of any nebulised antibiotic. The viability of this treatment option, however, needs further study given the fact that the chronic nature of NCFB begs the question “How viable is prolonged treatment in patients where PA resistance is increasing?” Further work is required to address and provide an evidence base for this.

The presence of PA is a crucial determinant for clinical outcomes in NCFB. CHALMERS *et al.* [39] have described a bronchiectasis severity index (BSI) score assessing disease severity, and this includes the presence of PA. This risk index will hopefully provide the ability to evaluate the viability of the treatment in colonised patients of differing severities. By standardising more heterogeneous groups of NCFB patients by severity, we could consider combined intravenous and inhaled antimicrobial regimens for PA eradication [40, 41]. Few studies to date have been performed to address this, and further work is necessary to better understand the role, function and behaviour of this microbe in NCFB [7, 14, 42, 43]. The use of antibiotics as a pre-emptive measure has itself been proven useful through some clinical trials [44]; however, the evaluated therapies require correlation with the BSI and future re-colonisation risk assessments.

What options do we have to prevent chronic PA colonisation?

NCFB patients are frequently colonised and/or infected with bacterial pathogens that induce local and (more rarely) systemic responses, which in turn drive airway inflammation and disease progression [45–47]. Of all bacteria, PA is by far the

most frequent and well-described coloniser, which associates with mortality, frequent exacerbations and a poorer quality of life [48–50]. If it were possible to prevent colonisation, we could have a significant impact on the quality of life in NCFB patients, their life expectancy, and associated healthcare system costs.

PA is a ubiquitous Gram-negative bacterium commonly encountered in the environment. The lung’s defences quickly clear it in healthy individuals [51]. Conversely, in NCFB patients, PA uses several immunomodulatory properties to facilitate its survival during acute lung infection (*i.e.* exacerbations) or, more importantly, during chronic lung bacterial colonisation [52]. PA possesses a single polar flagellum that binds to extracellular Toll-like receptor 5 and intracellular NOD-like receptors, which leads to the release of pro-inflammatory cytokines, facilitating neutrophil recruitment [51, 53]. However, in patients with a chronic lung infection, PA secretes bacterial proteases (*e.g.* AprA and LasB), which cleave extracellular flagellin, which in turn shuts down flagellin-mediated immune recognition.

Similarly, the downregulation of regulatory genes through mutation may attenuate flagellar expression and motility [54, 55]. Additionally, PA suppresses the type III secretion system (T3SS), which is the primary innate immune activator system; the suppression by PA results in dampened inflammasome activation and reduced pyroptotic cell death in macrophages and neutrophils [51, 56]. PA also produces proteases that degrade immunoglobulins and pro-inflammatory cytokines (*e.g.* interleukin (IL)-6 and interferon- γ), diminishes oxidative burst, and produces exopolysaccharides like alginate that interfere with opsonisation and phagocytosis including complement activation. Psl and Pel are critical factors for biofilm formation and represent viable targets for therapy [51, 57, 58]. In general, PA is capable of generating adaptive change facilitating immune evasion, allowing it to circumvent host defences and cause acute and chronic infections [59].

Based on the described mechanisms, PA can cause chronic colonisation in NCFB. Various approaches have attempted to employ these mechanisms to prevent colonisation. For instance, there has been development of antibacterial monoclonal antibodies to neutralise the bacteria’s virulence factors. DIGIANDOMENICO *et al.* [60], using an animal model, employed a monoclonal antibody directed to Psl that resulted in the opsonophagocytic killing of PA *in vitro* but, importantly, this antibody was also capable of inhibiting bacterial attachment to cultured lung epithelial cells. Then, in a multicentre randomised placebo-controlled trial, FRANÇOIS *et al.* [61] reported the use of another monoclonal antibody, this time directed against the T3SS, and showing that in treated patients lesser PA pneumonia is observed compared to placebo.

Other approaches include vaccine development, which has received significant research focus:

animal and clinical studies have been performed to evaluate mucosal immunisation against PA, with promising results [62]. For instance, YANG *et al.* [63] developed a trivalent vaccine using the outer membrane protein I, the haemolysin co-regulated protein 1 and PA V antigen (a component of the T3SS), which resulted in strong sustained immune responses, reduced bacterial loads, downregulated inflammatory cytokines and decreased inflammatory cell infiltration. Despite this, the translation of these findings into human applications remains uncertain [62].

While significant advances have been made in our understanding of PA pathogenesis, little advance has been made regarding therapeutic strategies in NCFB. Nevertheless, the emerging vaccine data are promising and should be pursued. If successful, a vaccine is likely to afford benefit not only to NCFB patients but also to those with COPD and/or cystic-fibrosis-related PA colonisation.

Does mortality differ between PA-colonised and non-colonised NCFB patients?

In a prospective study by LOEBINGER *et al.* [48], 91 NCFB patients were followed over 13 years to outline that PA was independently associated with mortality. In a retrospective cross-sectional analysis conducted by GOEMINNE *et al.* [64] in 539 NCFB patients, it was described that bacterial colonisation was associated with more deaths, higher exacerbation rates and reduced pulmonary function, in addition to a higher symptomatic burden. The two most common and prevalent bacteria described in this work were PA and *Haemophilus influenzae*, and patients with PA had worse lung function, which in itself is a factor for higher mortality. Importantly, however, infections with *Escherichia coli* and *Aspergillus* species also showed significant association with death [22–24, 64–66].

In more recent work, the derived and validated BSI indicates PA colonisation as a critical factor. Using Cox proportional hazard regression analyses for mortality and hospitalisation, CHALMERS *et al.* [39] illustrate that NCFB patients with PA colonisation have significant risks for hospitalisation and mortality. Using prospective analyses, GOEMINNE *et al.* [67] assessed overall death for all newly diagnosed patients (2006–2012) and the death rate was 20.4%; however, those with PA colonisation had higher rates.

The importance of PA in NCFB mortality was further confirmed in work by MARTÍNEZ-GARCÍA *et al.* [68], which developed the FACED score (which includes forced expiratory volume in 1 s, age, chronic colonisation by PA, extension of bronchiectasis, and dyspnoea). In this multicentre observational study, including 819 NCFB patients,

one of the key independent variables associated with 5-year all-cause mortality was the presence of PA colonisation. They also report persistent colonisation by multidrug-resistant Gram-negative bacilli, *Staphylococcus aureus*, atypical mycobacteria and fungi, but none of these presented any significant predictive power for mortality [68].

The currently available evidence favours mortality differences between NCFB patients colonised with PA and those without. The former should be promptly identified and treated according to current clinical guidelines [1, 5, 18, 19].

Is dual antibiotic therapy useful in patients with an acute exacerbation associated with PA?

While NCFB has gained worldwide recognition, one topic of particular clinical interest is how precisely to manage acute exacerbations [1]. However, different definitions of exacerbations have been used over the years in clinical trials. A recent publication, however, by an international group of investigators gathered at the first World Bronchiectasis Conference, proposed a consensus-based definition for exacerbations in bronchiectasis that addresses this issue. NCFB acute exacerbations were defined as a worsening in three or more of the following key symptoms for at least 48 h: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise and haemoptysis [15].

While most exacerbations are managed with antibiotics, patients with new isolation of PA in sputum should prompt eradication therapy because of the worse clinical prognosis associated with this organism [1, 6]. An alternative strategy to manage patients with exacerbations due to PA is comparable to that in cystic fibrosis, where two antipseudomonal antibiotics are concurrently employed, the rationale for which is that combined therapy improves treatment response and/or reduces the development of antibiotic resistance [69]. A double-blinded clinical trial conducted by BILTON *et al.* [70] included 53 patients with acute exacerbation due to PA infection and compared 14 days of therapy with ciprofloxacin with and without inhaled tobramycin *versus* placebo. The work found that dual therapy achieved a higher microbiological response, but no statistically significant differences in clinical outcomes were detectable, for either resolution of the exacerbation or improvement in symptoms. Therefore, while combination therapy is a logical alternative approach, the lack of statistical response in this study may be explained by the small sample size. Well-powered and well-designed studies accounting for NCFB heterogeneity are needed in future to better document the clinical benefit from such an approach.

In a separate trial from 2010 by HOSSAIN *et al.* [71] conducted in Dhaka (Bangladesh) with 65 patients, subjects were randomised into two groups: group A received nebulised gentamicin in addition to systemic antibiotics, and group B received systemic antibiotics with placebo nebulisation. Group A reported an enhanced recovery rate compared to group B; additionally, the researchers found that patients treated with two antibiotics had shorter lengths of hospital stay. Of note, this work did not explicitly mention whether patients had confirmed isolation of PA.

A Cochrane review from 2018 on the subject included only the two aforementioned clinical trials and concluded that evidence is insufficient to inform a robust conclusion and recommended further high-quality research be performed to determine the efficacy and safety of combination therapy [69]. Given this, it is essential to recognise the trial by TSCHUDIN-SUTTER *et al.* [72] in patients with systemic PA infection, including some with a respiratory source. It is not reported if any of these patients had NCFB but the study does conclude that a combination of beta-lactam with an aminoglycoside or quinolone therapy improved survival, independent of potential confounders including age, neutropenia and/or inadequate empirical treatment. Although this work did not focus on NCFB directly, it does illustrate that combination therapy may be useful, especially in severe infection.

Collectively, the evidence indicates that dual therapy is a promising avenue for the management of patients with PA-related exacerbations; however, before any firm conclusions and subsequent recommendations can be made, additional clinical trials and evidence are necessary to inform clinical practice. Finally, it is important to highlight that newer treatment alternatives, with novel methods of delivering anti-pseudomonal drugs, are available for clinical practice [73, 74]; however, further studies are needed to include them in daily patient care.

For how long should PA-related acute exacerbations of NCFB be treated?

In patients with NCFB, exacerbation frequency and severity have significant impact on quality of life, disease progression, morbidity and mortality [19]. Consequently, international guidelines directing treatment, such as the Spanish and British Thoracic Society guidelines, suggest a treatment course of 14 days with antibiotics to manage acute infectious exacerbations [75, 76]. These recommendations are further evidenced by findings in a series of small clinical trials. In 2009, MURRAY *et al.* [41] conducted a prospective study in 32 patients with acute NCFB exacerbations and reported that, following a 14-day course

of intravenous antibiotic treatment, patients had reduced sputum volume and markers of inflammation, better bacterial clearance, and an improved St George's respiratory questionnaire score. Importantly, this work failed to identify improvements in lung function, and no substantial difference was detected even after analysis following microbiological stratification.

In other work, CHALMERS *et al.* [47] illustrated in 34 acute NCFB exacerbations treated with intravenous antibiotics for a 14-day period that, following treatment, no significant bacterial growth was detected in sputum and this accompanied a reduction in airway inflammation (*i.e.* myeloperoxidase activity, neutrophil elastase, IL-8, tumour necrosis factor (TNF)- α and IL-1 β). It was observed that patients with PA had the highest levels of myeloperoxidase, IL-8 and TNF- α , and even after day 14, four patients continued to demonstrate significant airway growth of PA.

While the existing evidence base does suggest that patients with PA-related exacerbations benefit from prolonged courses of antibiotics (*i.e.* 14 days), no studies directly comparing short courses *versus* long antibiotic courses are available. Despite this, data extracted from the study by BILTON *et al.* [70] do not suggest any differences at 7 days with regard to airway bacteria load and lung function but, importantly, this work was not designed for such comparisons but rather for assessing combination *versus* monotherapy, potentially explaining the detected response. Assessing the available work only serves to further highlight the urgent need for clinical trials in patients with NCFB, exacerbations and PA-related infection.

Are there different endophenotypes of patients with NCFB?

One of the key issues highlighted from our prior proposed clinical questions is that current data in NCFB are heterogeneous in terms of patient populations, which in many cases has led to a lack of "strong recommendations" or consensus on the best treatment approaches for NCFB. Additionally, a failure to translate therapies successfully used in cystic fibrosis suggests differences in disease-driving mechanisms [3, 8]. Therefore, some researchers have proposed that the NCFB patient population is heterogeneous and consists of multiple clinical phenotypes that can be accompanied by one or more endotypes, disease-driving mechanisms that can occur alone or in combination. By identifying different disease phenotypes, individualised treatment may be offered to patients with likely improvement to clinical outcomes, in line with the developing applications of precision medicine to other respiratory disease states including severe asthma [9].

In work by ALIBERTI *et al.* [77], 1145 NCFB patients recruited from across Europe illustrated four clinical NCFB phenotypes, as follows. 1) Chronic infection with PA, which had the most severe disease, worst radiological pattern and greatest inflammatory responses, including frequent exacerbations, hospitalisations and worst quality of life [78]. 2) Chronic infection with pathogens, with moderate levels of systemic inflammation and functional status and where 20% experienced at least an annual exacerbation. 3) A group demonstrating daily sputum production, which was the largest cluster, with an absence of chronic infection but higher proportions of smokers or ex-smokers. 4) Finally, a “dry bronchiectasis” phenotype with the lowest levels of inflammatory cytokines, least radiological damage and less functional impairment. This latter group also had no chronic infection.

In addition, other important NCFB phenotypes have been proposed: a frequent exacerbation phenotype is described [79] and, in separate work [80], frequent exacerbators illustrate dysregulated levels of antimicrobial peptides including the cathelicidin LL-37 and secretory leukocyte protease inhibitors, which are associated with poorer lung function and PA infection [80].

More recently, endotypes (pathobiological mechanisms that drive NCFB) have gained research interest. MAC AOGÁIN *et al.* [9] hypothesised that allergic sensitisation in NCFB may associate with poor clinical outcome. Using patients across two continents, they illustrate that allergic sensitisation occurs at high frequency in NCFB and that patients with a sensitisation, induced by a range of allergens, may reflect either co-existing subclinical allergic airways disease or a predisposition to atopy. Importantly, they describe a group of NCFB patients with fungal sensitisation, which in patients with COPD is an established risk

factor for the development of bronchiectasis. Two “immunoallotypes” were described in this work, each accompanied by differing immune-inflammatory signatures: 1) a fungal-driven form, characterised by high concentrations of pro-inflammatory cytokines, and 2) a form associated with house dust mites, related to chemokine-dominant inflammation. This is the first possible description of endotypes in NCFB and acts as a platform for future work [9].

The above studies clearly illustrate the growing interest in phenotyping NCFB to improve clinical outcomes, which in turn may assist in identifying novel treatment approaches for particular patient subgroups in this heterogeneous disease. This is important, as no therapy is currently licensed for this devastating disease and it is unlikely that the “one size fits all” approach will work [3]. Precision approaches to NCFB are promising [81], remove the inherent disease heterogeneity and may get the right treatment to the right patient at the right time. Identifying and combining key pathobiological and clinical characteristics in NCFB to identify clinically relevant subgroups is a clear avenue for future bronchiectasis research.

Conclusions

NCFB is a heterogeneous disease with a significant impact on morbidity, mortality and patient quality of life. PA plays a critical role in disease course and prognosis and, while much has been learned over the past two decades, the currently available literature is limited and highlights the major gaps that continue to exist. Endophenotyping bronchiectasis to address its inherent heterogeneity is a promising avenue for future investment and research.

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Conflict of interest

None declared.

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Self-evaluation questions

1. NCFB is considered a reversible and curable disease.
 - a) True.
 - b) False.
2. Which of the following statements is true regarding non-pharmacological ACTs?
 - a) Postural drainage, albeit uncomfortable, is the best strategy to help reduce symptoms and future exacerbations.
 - b) Percussion and vibration techniques are mostly oriented towards patients with multiple comorbidities.
 - c) PEP has been shown to be superior to other ACTs with regard to mucus clearance.
 - d) Pulmonary rehabilitation and exercise, due to the hypothesised increased pulmonary demand, is the superior strategy when taking into account multiple comorbidities and is less invasive.
3. Regarding PA colonisation, which of the following statements is not true?
 - a) Patients with PA bronchial colonisation have been shown to have rapid clinical deterioration, regardless of the stage of the disease.
 - b) PA poses a higher risk of therapeutic failure, due to its broad resistance spectrum and its phenotypic response towards antibiotic therapy.
 - c) Significant numbers of studies have evidenced that there is no benefit from pre-emptive therapy towards PA colonisation.
 - d) The BSI is a useful tool whenever considering PA eradication based on patient history and symptoms.
4. Vaccines and monoclonal antibodies, although proven partially useful, lack the appropriate evidence to be considered an integral part of prevention of PA chronic colonisation in bronchiectasis patients.
 - a) True.
 - b) False.
5. Bacterial colonisation is directly correlated with higher mortality. Which of the following microorganisms is more closely associated with a higher predictive power towards patient death in NCFB?
 - a) *Escherichia coli*.
 - b) *Staphylococcus aureus*.
 - c) *Pseudomonas aeruginosa*.
 - d) *Haemophilus influenzae*.
 - e) Upper and lower respiratory tract virus.
6. Regarding dual antibiotic therapy, which of the following statements is true?
 - a) The use of a beta-lactam in combination with an aminoglycoside or quinolone is currently recommended in patients with NCFB with PA colonisation.
 - b) Nebulised gentamicin has proven useful in combination with systemic antibiotics, when treating PA-colonised patients.
 - c) There are statistical differences regarding symptoms and resolution of exacerbations when patients are treated with ciprofloxacin plus inhaled tobramycin.
 - d) Although dual antibiotic treatment for PA-associated exacerbations shows promising results, more studies need to be conducted to make further statements.
7. There is currently little to no evidence supporting longer cycles of antibiotic treatment regarding NCFB exacerbation.
 - a) True.
 - b) False.

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Suggested answers

1. b.
2. d.
3. c.
4. a.
5. c.
6. d.
7. a.

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