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Bronchiectasis in COPD: A New Phenotype of COPD with Particular Attention

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Abstract

Bronchiectasis in Chronic obstructive pulmonary disease (COPD) has been recognized as a potential new phenotype of COPD in recent years due to different clinical presentation, prognosis and treatment response. Broad application of CT scan significantly increased identification of bronchiectasis in COPDpatients. Although the exact mechanism of bronchiectasis development in COPD is lacking, the chronic airway inflammation, colonization of particular bacteria strain such as *P. aeruginosa* and continuous airway reconstruction may proceed to airway damage and following bronchiectasis. The significance of identifying bronchiectasis in COPD patients is to improve patients' management through more individualized treatment regimen. Given the poor prognosis in COPD patients with bronchiectasis and limited evidenced based clinical experience, it is therefore essential to have high quality clinical trials conducted in this group of patients.

Keywords: Chronic obstructive pulmonary disease; Bronchiectasis; World health organization; Inhaled corticosteroids

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease that severely threatens human health. As World Health Organization (WHO) has predicted, social and economic burden of COPD will rise to the fifth and COPD will become the third leading cause of death worldwide by 2030 [1]. It has been widely recognized that COPD is a complex syndrome with numerous pulmonary and extrapulmonary manifestations with heterogeneity among individuals. In the recent years, clinicians also proved that the heterogeneity of COPD is associated with different clinical outcomes including symptoms, exacerbations, responses to recommended therapy, decline of lung function and death [2]. The description of phenotypes in COPD gives us a new perspective on the classification of patients into distinct subgroups with different pathophysiologic mechanisms which may guide individualized therapies and achieve better prognosis.

Due to the growing use of high-resolution CT (HRCT) scanning, bronchiectasis has been increasingly diagnosed in patients with COPD. Since the first description of overlapping of bronchiectasis and COPD by Barker in 2002 [3], the rates of bronchiectasis shown on HRCT have been estimated ranging from 4% to 57.6% in COPD patients [4-8]. These researches raise awareness of a potential phenotype of COPD with certain distinct presence, prognosis as well as different implications of therapy. In global initiative for chronic obstructive lung disease(GOLD) report newly updated in 2014, bronchiectasis associated with longer exacerbations and increased mortality in COPD, has been added as an important comorbidity that might need different therapeutic regimen [9].

Prevalence of Bronchiectasis in COPD

The evidences of bronchiectasis in COPD patients had been found in several studies, however the rate of coexistence was still far from consistent. In primary care, C O'Brien firstly showed that there were 29% of COPD patients who were diagnosed with bronchiectasis showing predominantly tubular sign on HRCT (26.3% of them were finally confirmed after excluding those with forced expiratory volume in the first second (FEV1) over 80%) [7]. Similar result was demonstrated that the presence of bronchiectasis was 27% in COPD patients recently [8]. It has been revealed that bronchiectasis in COPD is associated with clinical outcomes. Patel IS found that 50% of COPD patients had bronchiectasis with high levels of local inflammatory cytokines production, lower airway bacterial colonization and longer symptom recovery time upon exacerbation [6]. Besides, severity of airflow obstruction and at least one hospital admission for exacerbations in the previous year were also associated with an elevated prevalence of bronchiectasis in moderate to severe COPD [5]. Of note, data from Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study showed lower prevalence of bronchiectasis than those from above studies. Only 4% in 2164 subjects had bronchiectasis. The possible reason was that bronchiectasis might have been excluded at study enrollment. However, the rate of bronchiectasis in COPD increased with GOLD stages in this cohort [4]. Furthermore, among mechanically ventilated COPD patients at a respiratory ICU, about 31% of patients had bronchiectasis which might increase the duration of ICU stay and hospitalization but no difference in mortality [10]. It should be noted that different phenotypes of bronchiectasis including tubular, cystic and varicose have been identified in COPD patients in these studies. Among them, bronchiectasis was commonly distributed in lower, bilateral lobes while central type was relatively rare [5,6]. In C O'Brien's study, 72% patients demonstrated tubular bronchiectasis on HRCT and for those with varicose (12.5%) or cystic (15.5%)

bronchiectasis, more severe impairment of FEV1 and more mucopurulent sputum production were observed [7]. Although the prevalence of bronchiectasis in COPD varies among different studies, it has shown that bronchiectasis was associated with different clinical manifestations, treatment and prognosis of COPD, which means a new phenotype of COPD has already been noticed with specific understanding and particular attention.

Potential Pathogenesis of Bronchiectasis in COPD

Both COPD and bronchiectasis are characterized by chronic airway inflammation, a consequence of mixed genetic and environmental effects. Multiple mechanisms such as deficiency of alpha-1-antitrypsin (AAT), disturbance of oxidation and antioxidation and airway remodeling contribute to the development of COPD. For bronchiectasis, airway obstruction and chronic infection are the main causes for disease progression. The exact role of bronchiectasis in COPD remains unclear despite of the potential clinical significance indicated previously. Whether this specific phenotype is the coexistence of two diseases or a unique presence caused by certain unknown mechanisms or consequence of COPD still needs further investigation.

The classical known mechanisms of these two diseases may help us find underlying possibilities of this phenotype. In fact, there is overlap in the pathology of COPD and bronchiectasis. In both conditions, neutrophils and T lymphocytes are the main inflammatory cells which can release protease and cause pulmonary damage [11]. In bronchiectasis, the hypothesis of "vicious cycle" describing recurrent chronic inflammation and infection on its pathogenesis has been well accepted [12]. Infective insult can initiated local neutrophil recruitment which can further lead to proteinase release, bronchial damage, impaired host defenses and bacterial colonization and finally causes bronchial dilation characterized by the deficiency of elastin and even destruction of muscle and cartilage. As for COPD, inhalation of cigarette smoke and noxious fumes results in dysfunction of mucociliary transport system and loss of tight connection of epithelial cells, which can also promote inflammatory reaction, bacterial infection and colonization [13]. Thus, repeated chronic infection and inflammation characterized by neutrophils and T lymphocytes infiltration along with possible genetic susceptibility are more likely to cause microbes persistent existence and further tissue damage and remodeling, then initiate and sustain the pathogenesis cycle of bronchiectasis in COPD patients.

Pseudomonas aeruginosa is an important pathologic bacteria in bronchiectasis and was associated with severity of the disease [14]. About 12-31% of bronchiectasis patients were colonized with *P. aeruginosa* which can adhere to airway mucosa, form protective biofilm resistant to antibiotics or immune cells and worsen the airway damage and dilation [15]. In COPD, *P. aeruginosa* has been isolated from 3-20% patients, especially in those with more severe conditions, exacerbations and worse outcomes [16-19]. Yet the relationship between *P.aeruginosa* and bronchiectasis in COPD has not been fully proved and no significant relevance was shown in previous studies [5,16]. Further well controlled clinical investigation is needed to confirm the result. On the other hand, it is suggested that certain unknown mechanisms independent of classical and overlapped pathogenesis of bronchiectasis and COPD might exist.

Moreover, bronchiectasis has been found in some patients with AAT deficiency [20]. Cuvelier et al. analyzed AAT genes in bronchiectasis patients and discovered a significant association between emphysema and bronchiectasis caused by overrepresentation of PI*Z alleles [21]. They suggested that bronchiectasis may be a consequence of emphysema in these patients rather than a primary effect. Another research included 74 patients with severe AAT deficiency partially approved their conclusion. [22] In this research, 70 subjects showed bronchiectatic changes and 27 of them had clinical significant bronchiectasis. The prevalence of bronchiectasis in lobes mostly affected by emphysema was higher. However, some patients with bronchiectasis did not demonstrated obvious emphysema.

It remains difficult to figure out the exact mechanisms of bronchiectasis in COPD. More well-designed clinical analyses targeted on this phenotype are expected. Although there are similar pathophysiological processes that these two diseases may overlap, preliminary studies have implied that there must be some unknown complex or independent interaction between them that warrants further exploration.

Clinical Features and Diagnosis of Bronchiectasis in COPD

Patients producing large volumes of sputum may have underlying bronchiectasis. The presence of purulent sputum reflects an increase in inflammatory mediators, and its development may identify the onset of bacterial exacerbation [9]. Patients without persistent purulent sputum or hemoptysis may also show bronchiectasis on CT imaging. Sometimes fixed moist rales can be heard. Bronchiectasis can further intensify pulmonary hypertension caused by COPD and leads to cor pulmonale or even heart failure [10]. Moreover, patients with bronchiectasis usually reflect an increase in both local and systemic inflammatory mediators which can deteriorate nutrition status [5,23].

The presence of bronchiectasis on CT scan in COPD patients may modulate exacerbations and affect the severity and frequency [24]. Coexistence with bronchiectasis could increase mortality, course of exacerbations as well as the duration of ICU stay and hospitalization in COPD patients [6,7,10,25,26].

Increasing evidences have been provided on microbiological features of COPD patients with bronchiectasis. The isolation rate of potential respiratory pathogens in these patients is higher [5]. The pathogen pattern commonly isolated from COPD patients slightly different from bronchiectasis. *P. aeruginosa* is one of the most common bacteria infecting bronchiectasis patients while it is not usually found in COPD patients except those severe ones or during exacerbations [27-29]. *P. Aeruginosa* colonization has also been associated with accelerated decline of lung function in bronchiectasis and exacerbations in COPD [30-33]. For COPD patients with bronchiectasis, this phenotype may indicate high possibility of potential colonization or infection with pathogens like *P. aeruginosa*. On the other hand, if a COPD patient has relatively mild airflow obstruction but organism patterns in bronchiectasis such as *P. aeruginosa* and Staphylococcus aureus are repeatedly isolated, it may suggest the possible coexistence of bronchiectasis. Yet no definite relevance between *P. aeruginosa* and bronchiectasis in COPD has been clinically confirmed, and it is unclear whether isolation of pathogen patterns including *P. aeruginosa* in these patients is induced by bronchiectasis or by this distinct phenotype.

A diagnosis of COPD requires spirometry test which confirms persistent airflow limitation with a post-bronchodilator FEV1/FVC<0.70 apart from clinical symptoms. Bronchiectasis (non-cystic

fibrosis bronchiectasis here) is usually diagnosed based on imaging findings (HRCT). Both spirometry confirmation and imaging findings of bronchiectasis are essential for this particular phenotype. But as we've discussed above, relationship between bronchiectasis and COPD and underlying mechanisms of bronchiectasis in COPD remain unclear. Factors such as immunodeficiency or airway inflammation and repeated infections may contribute to the development of bronchiectasis in COPD. While bronchiectasis caused by other etiologies in a nonsmoker leads to a fixed airway obstruction and, thus, lead to the diagnosis of COPD. So we could not certainly separate bronchiectasis in COPD from bronchiectasis as independent disease so far and the clinical differentiation of these two diseases still needs further investigation. While at current situation, differential diagnose should be considered based on specific well-known risk factors or etiologies of each disease together with different clinical onset and manifestation as well.

Therapy

GOLD added bronchiectasis as a comorbidity of COPD in 2014 version and suggested that: 1) For bronchiectasis in patients with COPD, treatment should be along conventional lines for bronchiectasis with the addition of usual COPD strategies where indicated. 2) For COPD in patients with bronchiectasis, COPD should be treated as usual, although some patients may need more aggressive and prolonged antibiotic therapy [9]. To date, no specific recommended therapy based on evidences for this phenotype has been documented.

Bronchodilators

Bronchodilators including long-acting and short-acting beta-adrenergic agonists (LABAs and SABAs) and long-acting muscarinic antagonists (LAMAs) are the main stream therapies for stable COPD patients. So far there is no randomized trials referring to a full evaluation on the effect of bronchodilators on bronchiectasis [34]. In previous studies, some patients with bronchiectasis exhibited increase in FEV1 and FVC after using inhaled bronchodilators including beta-adrenergic agonists and anticholinergics. Generally, inhaled bronchodilators are recommended for the prevention of possible bronchospasms caused by physiotherapy and aerosolized antibiotics in bronchiectasis [35]. Martínez-García et al recently reported that a formoterol-budesonide combined treatment significantly improved the symptoms and health-related quality of life scores in non-cystic fibrosis bronchiectasis compared with high-dose budesonide treatment [36]. Overall, we conclude that for COPD patients with bronchiectasis, bronchodilators are the mainstay treatment although it is unclear which choice or combination is superior to another.

Anti-inflammatory Agents

Corticosteroids

Inhaled corticosteroids (ICS) along with long-acting bronchodilators are recommended as first choice for patients in Group C and D in COPD [9]. ICS alone (such as fluticasone) has been shown reducing the sputum and the level of inflammatory mediators in non-CF bronchiectasis [37-39]. As mentioned above, medium-dose budesonide combined with formoterol increased cough-free days and quality of life in bronchiectasis patients [36], but the safety of ICS and its impact on infection and inflammation have not been well described. Further research is necessary to find out whether the routine use of ICS with LABA will improve the symptoms and prognosis of COPD patients with bronchiectasis, as well as the proper dose which balance the safety and therapeutic effect.

Macrolides

Macrolide has been proved to be an immune modulator on host inflammatory response which plays an important role in the development of both bronchiectasis and COPD. Macrolide also have anti-pseudomonal properties by suppressing expression of quorum sensing pathways and virulence factors of *P. aeruginosa* [40,41] Larger long-term clinical trials such as Effectiveness of Macrolides in patients with Bronchiectasis using Azithroymycin to Control Exacerbations (EMBRACE) [42], Bronchiectasis and Low-dose Erythromycin Study (BLESS) [43] and Bronchiectasis and Long-term Azithromycin Treatment (BAT) [44] all showed that patients with bronchiectasis can benefit from macrolides by reducing the rate of exacerbations, relieving the symptoms and improving quality of life. As to COPD, azithromycin and erythromycin has been shown to reduce exacerbation frequency and duration [45,46]. However, the potential adverse effects such as gastrointestinal disturbance and abnormal liver function should be taken into consideration while prescribing macrolides. Data from BLESS and BAT has demonstrated that long-term use of macrolides could increase the prevalence of macrolides-resistant pathogens [43,44]. Although evidence shows that both bronchiectasis and COPD patients benefits from macrolides, its effect on COPD patients with bronchiectasis is unclear. Further investigation focusing on this distinct phenotype is needed.

Phosphodiesterase 4 inhibitors

As an effective anti-inflammatory agent, roflumilast, the first oral phosphodiesterase 4 (PDE4) inhibitor, has been shown to reduce exacerbation frequency in a subgroup of COPD patients who suffered from chronic sputum production with severe to very severe FEV1 [47]. The isolation of a potential pathogenic microorganism from the sputum of a patient with stable COPD, together with a FEV1<50% predicted and at least one hospital admission for exacerbation in the previous year were associated with a 99% probability of having bronchiectasis on CT scan [5]. Thus, we speculate that in the study of roflumilast, although CT scan was not performed, there might be COPD patients with bronchiectasis who benefited from this therapy. Further research is expected to demonstrate the exact response of COPD patients with bronchiectasis to PDE4 inhibitors.

Antibiotics

Usually, antibiotics are not indicated for stable COPD patients. For those with infectious exacerbations and other bacterial infections, the recommended length of antibiotic therapy is usually 5-10 days [9]. In bronchiectasis, antibiotics are used in the following scenarios: (1) to eradicate *P. aeruginosa* and/or methicillin-resistant Staphylococcus aureus (MRSA), (2) to suppress the burden of chronic bacterial colonization, or (3) to treat exacerbations [34]. Eradication of pathogenic bacteria and suppressive antibiotic therapy has been shown to reduce airway and systemic inflammatory mediators, lower bacterial burden and decrease the exacerbation frequency in bronchiectasis [48,49]. Inhaled or long-term antibiotics are recommended for patients having three or more exacerbations per year and for those during exacerbations, a 14 days of antibiotic therapy is recommended [50]. For COPD patients with bronchiectasis, the possible pathogen

pattern of bronchiectasis should be taken into consideration when using antibiotics during an acute exacerbation, although the exact duration of antibiotic use is still inconclusive at present. However, it's believed that clinical success of antibiotic and its duration should be determined according to improvement of patients' symptoms or signs as well as laboratory test results during exacerbations. On the other hand, further studies are also expected to determine whether it is necessary to treat this phenotype with long-term oral or inhaled antibiotics therapy to prevent exacerbations, reduce bacterial colonization and load.

Conclusions

Bronchiectasis in COPD may represent a newly recognized phenotype confirmed by increasing use of HRCT in recent years. As mentioned above, it has been suggested that this phenotype is associated with critical clinical outcomes of COPD such as severe airflow obstruction, isolation of pathogenic organisms, exacerbations and mortality, which reminds us that we may need to pay specific attention to its pathogenesis, clinical features and treatment. We briefly summarized and discussed main current findings and potential interest of further research. Notwithstanding an increased recognition of this distinct phenotype, there are limited trials and researches that reveal the underlying relationship or interaction between bronchiectasis and COPD, as well as the exact prognosis and specific therapies targeted at these patients. Well designed studies are expected to provide more evidence in the future.

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References

1. Website of World Health Organization.
2. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, et al. (2010) Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 182: 598-604.
3. Barker AF (2002) Bronchiectasis. N Engl J Med 346: 1383-1393.
4. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, et al. (2010) Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 11: 122.
5. Martínez-García MÁ, Soler-Cataluña JJ, Donat Sanz Y, Catalán Serra P, Agramunt Lerma M, et al. (2011) Factors associated with bronchiectasis in patients with COPD. Chest 140: 1130-1137.
6. Patel IS, Vlahos I, Wilkinson TM, Lloyd-Owen SJ, Donaldson GC, et al. (2004) Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170: 400-407.
7. O'Brien C, Guest PJ, Hill SL, Stockley RA (2000) Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. Thorax 55: 635-642.
8. Bafadhel M, Umar I, Gupta S, Raj JV, Vara DD, et al. (2011) The role of CT scanning in multidimensional phenotyping of COPD. Chest 140: 634-642.
9. GOLD Executive Committee. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease .
10. Gursel G (2006) Does coexistence with bronchiectasis influence intensive care unit outcome in patients with chronic obstructive pulmonary disease? Heart Lung 35: 58-65.
11. King PT (2009) The pathophysiology of bronchiectasis. Int J Chron Obstruct Pulmon Dis 4: 411-419.
12. Cole PJ (1986) Inflammation: a two-edged sword--the model of bronchiectasis. Eur J Respir Dis Suppl 147: 6-15.
13. Hogg JC (2004) Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 364: 709-721.
14. Whiteley M, Bangera MG, Bumgarner RE, Parsek MR, Teitzel GM, et al. (2001) Gene expression in Pseudomonas aeruginosa biofilms. Nature 413: 860-864.
15. Pappalettera M, Aliberti S, Castellotti P, Ruvolo L, Giunta V, et al. (2009) Bronchiectasis: an update. Clin Respir J 3: 126-134.
16. Garcia-Vidal C, Almagro P, Romaní V, Rodríguez-Carballeira M, Cuchi E, et al. (2009) Pseudomonas aeruginosa in patients hospitalised for COPD exacerbation: a prospective study. Eur Respir J 34: 1072-1078.
17. Almagro P, Salvadó M, Garcia-Vidal C, Rodríguez-Carballeira M, Cuchi E, et al. (2012) Pseudomonas aeruginosa and mortality after hospital admission for chronic obstructive pulmonary disease. Respiration 84: 36-43.
18. Groenewegen KH, Wouters EF (2003) Bacterial infections in patients requiring admission for an acute exacerbation of COPD; a 1-year prospective study. Respir Med 97: 770-777.
19. Patel IS, Seemungal TA, Wilks M, Lloyd-Owen SJ, Donaldson GC, et al. (2002) Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. Thorax 57: 759-764.
20. Shin MS, Ho KJ (1993) Bronchiectasis in patients with alpha 1-antitrypsin deficiency. A rare occurrence? Chest 104: 1384-1386.
21. Cuvelier A, Muir JF, Hellot MF, Benhamou D, Martin JP, et al. (2000) Distribution of alpha(1)-antitrypsin alleles in patients with bronchiectasis. Chest 117: 415-419.
22. Parr DG, Guest PG, Reynolds JH, Dowson LJ, Stockley RA (2007) Prevalence and impact of bronchiectasis in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med 176: 1215-1221.
23. Hill AT, Bayley D, Stockley RA (1999) The interrelationship of sputum inflammatory markers in patients with chronic bronchitis. Am J Respir Crit Care Med 160: 893-898.
24. Wedzicha JA, Hurst JR (2007) Structural and functional co-conspirators in chronic obstructive pulmonary disease exacerbations. Proc Am Thorac Soc 4: 602-605.
25. Martínez-García MA, de la Rosa Carrillo D, Soler-Cataluña JJ, Donat-Sanz Y, Serra PC, et al. (2013) Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 187: 823-831.
26. Fujimoto K, Kitaguchi Y, Kubo K, Honda T (2006) Clinical analysis of chronic obstructive pulmonary disease phenotypes classified using high-resolution computed tomography. Respirology 11: 731-740.
27. Pasteur M C, Bilton D, Hill AT (2010) British Thoracic Society guideline for non-CF bronchiectasis J Thorax 65: 577.
28. Wilson R (2001) Bacteria, antibiotics and COPD. Eur Respir J 17: 995-1007.
29. Rosell A, Monsó E, Soler N, Torres F, Angrill J, et al. (2005) Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. Arch Intern Med 165: 891-897.
30. Murphy TF, Brauer AL, Eschberger K, Lobbins P, Grove L, et al. (2008) Pseudomonas aeruginosa in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 177: 853-860.
31. Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, Román-Sánchez P, Soriano J (2007) Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest 132: 1565-1572.

32. Divangahi M, Matecki S, Dudley RW, Tuck SA, Bao W, et al. (2004) Preferential diaphragmatic weakness during sustained Pseudomonas aeruginosa lung infection. Am J Respir Crit Care Med 169: 679-686.
33. Williams BJ, Dehnbostel J, Blackwell TS (2010) Pseudomonas aeruginosa: host defence in lung diseases. Respirology 15: 1037-1056.
34. McShane PJ, Naureckas ET, Tino G, Strek ME (2013) Non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 188: 647-656.
35. Martínez García MÁ, Máiz Carro L, Catalán Serra P (2011) [Treatment of non-cystic fibrosis bronchiectasis]. Arch Bronconeumol 47: 599-609.
36. Martínez-García MÁ, Soler-Cataluña JJ, Catalán-Serra P, Román-Sánchez P, Tordera MP (2012) Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. Chest 141: 461-468.
37. Tsang KW, Tan KC, Ho PL, Ooi GC, Ho JC, et al. (2005) Inhaled fluticasone in bronchiectasis: a 12 month study. Thorax 60: 239-243.
38. Martínez-García MA, Perpiñá-Tordera M, Román-Sánchez P, Soler-Cataluña JJ (2006) Inhaled steroids improve quality of life in patients with steady-state bronchiectasis. Respir Med 100: 1623-1632.
39. Tsang KW, Ho PL, Lam WK, Ip MS, Chan KN, et al. (1998) Inhaled fluticasone reduces sputum inflammatory indices in severe bronchiectasis. Am J Respir Crit Care Med 158: 723-727.
40. Tateda K, Ishii Y, Kimura S, Horikawa M, Miyairi S, et al. (2007) Suppression of Pseudomonas aeruginosa quorum-sensing systems by macrolides: a promising strategy or an oriental mystery? J Infect Chemother 13: 357-367.
41. Whitters D, Stockley RA (2013) Bronchiectasis in older patients with chronic obstructive pulmonary disease : prevalence, diagnosis and therapeutic management. Drugs Aging 30: 215-225.
42. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, et al. (2012) Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet 380: 660-667.
43. Serisier DJ, Martin M L, Mcguckin M A (2013) Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial J JAMA 309: 1260-1267.
44. Altenburg J, de Graaff CS, Stienstra Y (2013) Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. J JAMA 309: 1251-1259.
45. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, et al. (2011) Azithromycin for prevention of exacerbations of COPD. N Engl J Med 365: 689-698.
46. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, et al. (2008) Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med 178: 1139-1147.
47. Rennard SI, Calverley PM, Goehring UM, Bredenbröker D, Martinez FJ (2011) Reduction of exacerbations by the PDE4 inhibitor roflumilast--the importance of defining different subsets of patients with COPD. Respir Res 12: 18.
48. White L, Mirrani G, Grover M, Rollason J, Malin A, et al. (2012) Outcomes of Pseudomonas eradication therapy in patients with non-cystic fibrosis bronchiectasis. Respir Med 106: 356-360.
49. Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, et al. (2012) Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 186: 657-665.
50. Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group (2010) British Thoracic Society guideline for non-CF bronchiectasis. Thorax 65 Suppl 1: i1-58.