View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Diposit Digital de Documents de la UAB

LONG-TERM AZITHROMYCIN THERAPY IN PATIENTS WITH SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND REPEATED PULMONARY EXACERBATIONS

ABSTRACT

Rationale: Long-term macrolide therapy can result in clinical improvement in patients with severe chronic inflammatory lung diseases associated with frequent bacterial colonization and chronic infection.

Objective: To determine wether long-term azithromycin therapy reduces exacerbation frequency in severe chronic obstructive pulmonary disease (COPD)

Methods: Retrospective observational study to assess the clinical benefits of long-term azithromycin therapy (500 mg orally three times per week) over 12 months in severe COPD patients with a minimum of 4 acute exacerbations (AECOPD) per year or colonized by *Pseudomonas aeruginosa* and comparing with the previous 12 months: the number of AECOPD, hospitalizations and days of hospital stay. Patients were classified into three groups according to the previous baseline colonization: group 1, common microorganisms; group 2, colonized by *P.aeruginosa* and group 3 alternate common microorganisms and *P.aeruginosa.*

Measurments and main results: We include 24 patients, all men, mean (SD) age 70.9 (7.4) years, FEV1 0.95 L (32.2%). The patients had 7.0 (3.0) AECOPD, 3.3 (2.0) hospitalizations and 43.0 (26.2) days of hospital stay in the year before recruitment. Four patients did not complete the 12 months of treatment, only one had to be withdrawn related to side effects (dyspepsia). We analyzed 20 patients who completed the year of treatment (35% group 1, 45% group 2 and 20% group3). Long-term azithromycin therapy reduced significantly (year before versus year with azithromycin): AECOPD 6,8 (2,8) vs 2,8 (2,5) p=0,000; hospitalizations 3,6 (1,4) vs 1,4 (1,5) p=0,001 and days of hospital

stay 43,7 (21,4) vs 25 (32,2) p=0,013. Analyzing by subgroups the improvement was particularly significant in group 1 patients with common microorganisms with a 70% reduction in AECOPD and hospitalizations. Group 2 and 3 also improved highlighting those colonized by *P.aeruginosa* with 43% and 47% reduction in AECOPD and hospitalizations respectively.

Conclusions: Long-term azithromycin is associated with a significant reduction of AECOPD, hospitalizations and days of hospital stay in patients with severe COPD and repeated AECOPD independently to baseline colonization.

INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is associated with the presence of acute exacerbations (AECOPD) [1] . Mortality risk increases with the frequency of AECOPD especially when patients require hospitalization [2, 3]. Bacterial infections are likely etiologic for approximately 50% of AECOPD [4]. Recently there has been greater interest in the use of prophylactic antibiotics to prevent AECOPD [5]. Macrolides have both antibacterial and antiinflamatory properties. Long-term macrolide therapy is routinely used in two diseases that involve chronic airway inflammation such as diffuse panbronchiolitis and cystic fibrosis (CF). In diffuse panbronchiolitis, erythromycin has been the most commonly used macrolide, showing remarkably improvement in survival and symptoms [6]. Studies in CF have used mostly azithromycin showing improvements in lung function and reduction in exacerbation frequency [7, 8], the effect is probably due to modulation of the inflammatory response and the ability of azithromycin to impede biofilm formation being recommended in chronic bronchial infection by *Pseudomonas* species [9] [10].

Given the importance of inflammation [11] and bacterial infection in the pathogenesis of COPD it has been proposed that macrolides may offer unique advantages as disease modifying agents. There are only two studies that analyze the effectiveness and safety of long-term erithromycin in COPD over a periods of 12 months with a significant reduction in moderate to severe AECOPD [12, 13]. Remains to be defined if the terapeutic effect reflect antimicrobial activity, an immunomodulatory effect, or both.

Azithromycin, the prototypical 15 member-ring macrolide, appears to have a better safety profile and dosage for its long-term use as well as improved bacteriological activity, especially in bronchial colonization by *P.aeruginosa*, with regards to erythromycin.

We report in this article the usefulness of long-term azithromycin therapy to reduce exacerbation frequency in severe COPD patients that despite being treated maximally with conventional therapies are in high-risk of AECOPD; the therapeutic effect according to baseline colonization by *P.aeruginosa* or common microorganisms and its impact on bacteriology and development of resistance to macrolides.

Key words: *Macrolides,* Azithromycin*, COPD exacerbation.*

METHODS

Retrospective observational study in patients with severe COPD controlled in the respiratory day hospital of the Sabadell hospital (Barcelona, Spain) (March 2007-August 2009) to assess the clinical benefits of long-term azithromycin therapy (500 mg orally three times per week) for 12 months to reduce AECOPD frequency.

The inclusion criteria were patients with severe COPD (FEV1< 50% of predicted) with a minimum of 4 AECOPD in the year prior to start azithromycin or patients with chronic bronchial colonization by *P.aeruginosa.*

Patients with asthma, bronchiectasis, malignancies, unstable heart disease or liver disease were excluded. In the recruitment pulmonary function tests and oxygen therapy at home were noted. All patients underwent the same clinical control in the respiratory day hospital before and after starting long-term azithromycin and all were treated with long-term beta-agonists, anticholinergics and inhaled corticosteroids. Colimycin inhaled therapy was noted in those with chronic colonization by *P.aeruginosa* .

Patients were classified into three groups according to the potentially pathogenic microorganisms (ppm) isolated from sputum samples during the AECOPD in the year prior to start azithromycin: Group 1, patients with common microorganisms (*Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis*); group 2, patients with chronic bronchial colonization by *P.aeruginosa* and group 3 patients that alternate common microorganisms and *P aeruginosa* but without bronchial colonization.

We compare the period of 12 months of treatment with azithromycin with the previous 12 months, overall and by groups, the following parameters: number of

AECOPD, hospitalizations and days of hospitalization for AECOPD. It also discusses the evolution of bacterial infection in each group and the development of resistance of ppm to azithromycin before and after long-term therapy with azithromycin.

Definition and treatment of exacerbations:

AECOPD is defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day to day variations, that is acute in onset and necessitates a change in regular treatment (oral corticosteroids and/or antibiotics and/or hospital admission) in a patient with underlying COPD [14]. AECOPD were attended from Monday to Friday (8:00 to 17:00 hours) at the respiratory day hospital always by the same team of pulmonologists [15]. Outside these hours AECOPD were attended in the emergency department with the reviewing of the emergency reports.

Definition of chronic bronchial colonization by P.aeruginosa:

Presence of three or more consecutive sputum cultures of *P.aeruginosa* isolated in a period of 6 months, in samples separated by at least 1 month in clinically stable patients [16] .

Statistical analysis:

Quantitative variables are expressed as mean ± standard deviation. Statistical analysis is performed using Student t test for paired data. All statistical tests were performed with a confidence level of 95%.

Results:

We include 24 patients with severe COPD, all men, mean age (SD) 70.9 (7.4) years. Pulmonary function tests showed, mean (% predicted), FVC 2.43 liters (58.8%), FEV1 0.95 liters (32.2%), and FEV1/FVC ratio 39%. Five patients (20.8%) used chronic domiciliary oxygen therapy.

In the 12 months prior to the start of azithromycin these patients had a mean (SD) of 7.0 (3.0) AECOPD, 3.3 (2.0) hospitalizations and 43.0 (26.2) days of hospital stay. Four patients did not complete 12 months with azithromycin. Of these four one was withdrawn for dyspepsia, one for diagnosis of malignancy during the follow-up and the other two discontinued the treatment unrelated to side effects.

We analyze the twenty patients who completed 12 months of treatment with azithromycin . In the 12 months prior to the start of azithromycin these patients had a total of 136 AECOPD, of which 72 (52,9%) were severe requiring hospitalization. Long-term azithromycin therapy resulted in a significant reduction of AECOPD and hospitalizations by a total of 57 and 28 respectively which represents an average reduction of 58.9% AECOPD and 61.2% hospitalizations; together with a reduction of 18.7 days in the mean hospital stay (See table I).

According to the ppm isolated in sputum samples during the year prior to start azithromycin 7 patients were included in group 1 with *common microorganisms,* 9 patients in group 2 with chronic bronchial colonization by *P.aeruginosa* (of these 5 (55,5%) were in colimycin inhaled therapy) and 4 patients in group 3 alternating common microorganisms and *P.aeruginosa.* Long-term azithromycin therapy reduced in all groups the number of AECOPD, hospitalizations and

days of hospital length stay. This reduction was particularly significant in the group of *common* microorganisms with a 70% reduction of AECOPD and hospitalizations; and reduction of 25 days in the mean hospital stay. In the *P.aeruginosa* group a statistically significant reduction in AECOPD of 43,5% was also observerd and in terms of hospitalizations and hospital stay despite a decrease of 47,1% and 32,5% respectively these not reach statistical significance. The alternating group improved in all parameters studied, althoug their small size did not allow statistically significant differences (See table I).

Variable		0-12 months WITHOUT AZITHROMYCIN		12-24 months WITH AZITHROMYCIN			
GLOBAL	**N**	**Total**	**Mean ± sd**	**Total**	**Mean ± sd**	**Red %**	**p**
Number of exacerbations	20	136	6.8 ± 2.8	57	2.8 ± 2.5	*58,9*	***0.000***
Number of hospitalizations	20	72	3.6 ± 1.9	28	1.4 ± 1.5	61,2	***0.001***
Days of hospital stay	20	874	43.7 ± 21.4	500	25.0 ± 32.2	42,8	***0.013***
COMMON MICROORGANISMS		**Total**	**Mean ± sd**	**Total**	**Mean ± sd**	**Red %**	**p**
Number of exacerbations	7	63	9.0 ± 2.3	19	2.7 ± 2.2	70	***0.00***
Number of hospitalizations	7	29	4.1 ± 2.6	9	1.2 ± 1.4	70,8	***0.04***
Days of hospital stay	7	309	44.1 ± 17.5	133	19 ± 25	57	***0.05***
PSEUDOMONAS AERUGINOSA		**Total**	**Mean ± sd**	**Total**	**Mean ± sd**	**Red %**	**p**
Number of exacerbations	9	42	4.6 ± 2.2	24	2.6 ± 2.0	43,5	***0.04***
Number of hospitalizations	9	31	3.4 ± 1.6	17	1.8 ± 1.7	47,1	*0.08*
Days of hospital stay	9	454	50.4 ± 23.9	306	34.0 ± 38.5	32,5	*0.23*
ALTERNATE		**Total**	**Mean ± sd**	**Total**	**Mean ± sd**	**Red %**	**p**
Number of exacerbations	4	31	7.7 ± 0.5	14	3.5 ± 4.4	54,6	*0.14*
Number of hospitalizations	4	12	3.0 ± 1.4	2	0.5 ± 1.0	83,3	*0.09*
Days of hospital stay	4	111	27.7 ± 17.0	61	15.2 ± 30.5	45,2	*0.27*

TABLE I: Number of AECOPD, hospitalizations and days of hospitalization with and without azithromycin, globally and according to the group of potentially pathogenic microorganisms (ppm) isolated from sputum samples before and initiation of azithromycin. (*N: Number of patients; SD: Standard derivation; % Red: Percentage of reduction).*

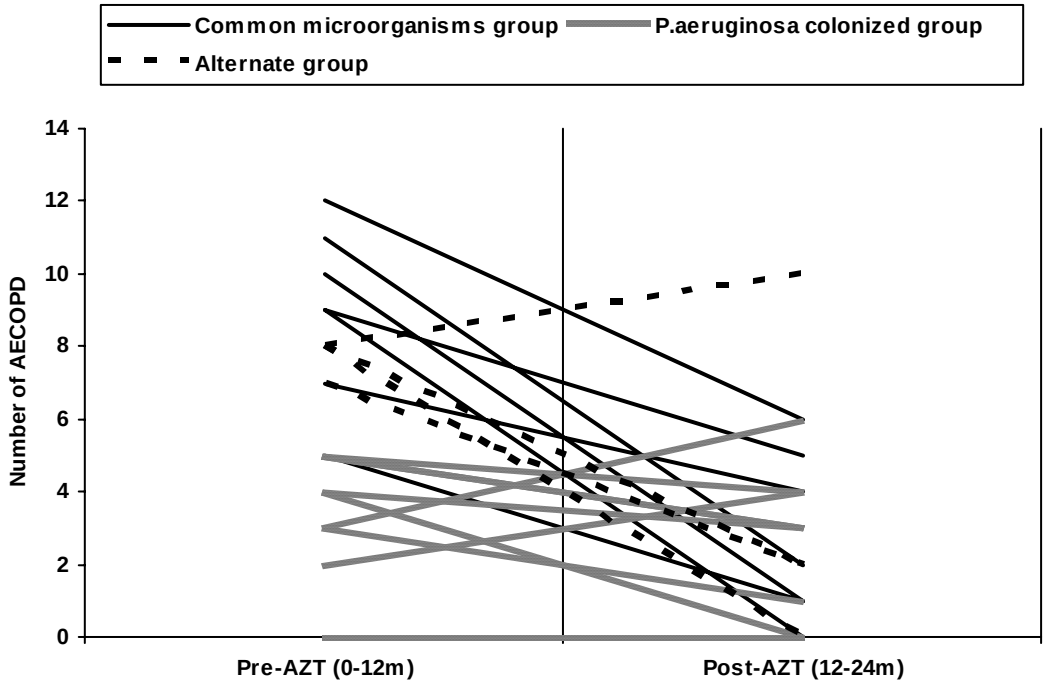

Figure I: Number of AECOPD before and after long-term azithromycin according to the group of potentially pathogenic microorganisms (ppm) isolated from sputum *(Pre-AZT: Before long-term azithromycin, Post AZT:After long-term azithromycin).*

Long term azithromycin therapy negativized the sputum cultures in 9 of 20 patients during follow-up; 4 corresponded to the common microorganisms group, 4 corresponded to the chronic bronchial colonization by *P aeruginosa* group, without significant association to the presence of mucoid forms or to be in colimycin inhaled therapy, and 1 to the alternating group. Azithromycin eradicated the common microorganisms in the alternating group, being observed in 3 of the 4 patients only *P aeruginosa* isolates during the follow-up with long-term azithromycin. In only 1 patient of common microorganisms group *P aeruginosa* was isolated during long-term azithromycin therapy (See table II).

		12-24 months WITH AZITHROMYCIN			
		NEGATIVE CULTURES	***COMMON MICROORGANISMS***	***P. AERUGINOSA***	**TOTAL**
0-12 months WITHOUT AZITHROMYCIN	***COMMON MICROORGANISMS***	4	2	1	7
	P. AERUGINOSA	4	0	5	9
	ALTERNATE	1	0	3	4
	TOTAL	9	2	9	20

TABLE II: Classification of patients according to the group of potentially pathogenic microorganisms (ppm) isolated from sputum samples before and after initiation long-term azithromycin therapy.

AECOPD with sputum culture isolates of common microorganism were reduced from 31 (22,7%) of a global 136 to 5 (8,7%) of a global 57 AECOPD during long-term azithromycin therapy.

In Table 3 we can see the sensitivity of common microorganisms to macrolides before and after long-term azithromycin therapy. Of note that all strains of *H.influenzae* isolated were resistant to erythromycin whereas none was against azithromycin before starting treatment and that the strains of *S.pneumoniae* resistant to macrolides were also resistant to clindamycin showing a highly resistant phenotype.

Regarding the bactericidal effect of long-term azithromycin therapy on common microorganisms and the development of bacterial resistance against it, we did not observe any isolate of *Mcatharralis* during the follow-up, a single isolate of *H.influenzae* that had developed resistance to azithromycin and four isolates of *S.pneumoniae* all resistant to azithromycin.

0-12 months WITHOUT AZITHROMYCIN	Erythromycin			Clarithromycin			Azithromycin			
	SEN	INT	RES	SEN	INT	RES	SEN	INT	RES	Nº isolates pre-AZT
Haemophilus influenzae	0	0	10	7	2	1	10	0	0	10 (31,3%)
Streptococcus pneumoniae	3	0	3	3	0	3	3	0	3	6 (18,8%)
Moraxella catharralis	14	1	1	15	0	1	15	0	0	15 (50%)
12-24 months WITH AZITHROMYCIN	**Erythromycin**			**Clarithromycin**			**Azithromycin**			
	SEN	INT	RES	SEN	INT	RES	SEN	INT	RES	Nº isolates post-AZT
Haemophilus influenzae	0	0	1	0	0	1	0	0	1	1 (20%)
Streptococcus pneumoniae	0	0	4	0	0	4	0	0	4	4 (80%)
Moraxella catharralis	0	0	0	0	0	0	0	0	0	0

TABLE 3: Common microorganisms isolated in sputum cultures during exacerbations before and after starting Azithromycin and its antibiogram to macrolides *(SEN: Sensitive, INT: intermediate, RES: resistant, Nº isolates pre-AZT: Number of isolates previous azithromycin therapy, Nº isolates post-AZT: Number of isolates post azithromycin therapy)*

Discusion:

This is the first study that evaluates the usefulness of long-term azithromycin therapy, for a period of 12-months, in patients with severe COPD and repeated AECOPD to reduce the exacerbation frequency and its therapeutic effect according to baseline colonization.

The weekly dosage of azithromycin used, one tablet of 500 mgr three times a week (monday, wednesday and friday) is the standard used in patients with bronchiectasis associated to Cystic fibrosis and chronic bronchial colonization by Pseudomonas aeruginosa [17].

Our results show that long-term azithromycin therapy in patients with severe COPD and repeated AECOPD reduce very significantly to less than half the number of AECOPD and hospitalizations and secondarily the days of hospital stay. The treatment was well tolerated over the 1-year period of treatment having to be removed in only one patient for dyspepsia.

The potential utility of long-term macrolide therapy in COPD is supported mainly by two published studies, both with erythromycin and for a period of 12 months, with a significant reduction in the number and severity of the AECOPD [12, 13]. First, Suzuki and colleagues reported results of an open-label, prospective randomized trial (not blinded) of erythromycin therapy (200-400mgr/day) versus non active treatment for twelve months in 109 COPD patients (FEV1=1,4 liters); they found an increased relative risk of experiencing an AECOPD in the control group versus erythromycin group of 4.71 (95% CI, 1.53 to 14.5; p = 0.007) and more severe AECOPD in the control group than in the erythromycin group (p = 0.0007). Second, Seemungal and colleagues, in a single-center, randomized

controlled trial, administered erythromycin (250 mg, twice daily) or placebo for 1 year to 109 patients with moderate to severe COPD (mean FEV_1 = 50% of predicted). The primary outcome was the frequency of AECOPD that required antibiotics, oral corticosteroids, or hospitalization. Erythromycin reduced AECOPD in relative terms by 35% and increased median time to first exacerbation from 89 to 271 days, both differences being statistically significant. All patients included in our study had severe COPD with a minimum of four AECOPD during the year prior to start azithromycin while Semungal and colleagues included patients with moderate to severe COPD, of them only 35% had three or more AECOPD during the year prior to inclusion.

In our opinion azithromycin offers clinical advantages over erythromycin. Regarding its metabolism doesn't interfere with the metabolic pathway of cytochrome P450 , which prevent possible metabolic interferences with other drugs that share the same pathway and are often used in COPD such as steroids and theophylline; has better digestive tolerance; has less hepatotoxicity and it isn't associated with long QT syndrome what makes it better tolerated with a better safety profile and dosage for its long-term use [18, 19]. Despite macrolides provide adequate coverage for the most frequently common microorganisms identified in AECOPD there are differences in *H.influenzae* activity. Azithromycin, the prototypical 15 member ring macrolide, appears to have improved bacteriological and clinical activity relative to 14-membered ring macrolides such as erithromycin and clarithromycin [20]. Observe that in our study all strains of *H.influenzae* isolated previous to start long-term azithromycin were resistant to erithromycin while none to azithromycin.

The subgroup analysis shows that those patients with AECOPD for common microorganisms (Group 1), despite being the group with a greater number of AECOPD and hospitalizations prior to start azithromycin, are the group that improved more with long-term azithromycin therapy by a very significant 70% reduction in AECOPD and hospitalizations. The mechanism of improvement could be related to the antibacterial activity of azithromycin particularly with regards to *H.influenzae* and *M.catharralis*, AECOPD with isolates for these microorganisms were reduced from a total of 25 pre-azithromycin to just one for *H.influenza* during long-term azithromycin therapy. We did not observe this level of bacterial erradication for *S.pneumoniae* with higher prevalence of resistance to azithromycin. However we can not exclude that the improvement observed may be due in part to anti-inflammatory and immunomodulatory properties of azithromycin [21]. Azithromycin could decrease the sputum volume and its viscoelasticity and increase mucociliary transport [22, 23]. Refer also the ability of azithromycin to accumulate in the neutrophil interfering with chemotaxis to the inflammatory focus and promoting neutrophil apoptosis and clearance by macrophages [24, 25]. Seemungal et al in its trial with long-term erithromycin analyzed as secondary outcomes inflammatory mediators in sputum (IL-6, IL-8 and myeloperoxidase) and plasma (IL-6, IL-8 and C-reactive protein) without finding no statistically significant treatment-related differences [13]. Lack of an erythromycin effect on inflammatory markers suggests that antimicrobial effects might be the more important. However, no causal linkage has been established between the inflammatory markers measured in this study and exacerbation frequency.

Patients with more advanced COPD and specially those with repeated courses of antibiotic therapy, hospital admisions or oral corticosteroids have an increased risk of exacerbations caused by *P.aeruginosa* [26, 27]. This is important because antibiotic treatment decisions should be stratified according to the severity of AECOPD with risk factors for *P.aeruginosa* isolation [28].

When analyzing our patients with chronic bronchial colonization by *P.aeruginosa* (group 2) these represent 45% of patients included wich reflects the severity of COPD. In these patients long-term azithromycin therapy improved all the outcomes analyzed by a statistically significant 43% reduction in AECOPD. Hospitalizations and days of hospital stay were also reduced to 47% and 32% respectively although not reach statistical signification.

It is known the role of macrolides, mainly azithromycin, in the treatment of chronic bronchial colonization by *P.aeruginosa* in patients with bronchiectasis, especially those associated with cystic fibrosis [7, 29]. Azithromycin interferes with *P.aeruginosa* quorum sensing and its production of virulence factors [30]; reduces biofilm formation by inhibiting alginate production and decreases bacterial adherence [31]. For these reasons we think that long-term azithromycin is also specially indicated in these group of patients. The reduction in hospitalizations and days of mean hospital stay is less evident in these group of patients because often require hospitalization to receive parenteral antibiotics due to *P.aeruginosa* resistance to oral antibiotics. Interestingly in 4 of these 9 patients colonized there were no isolates in sputum samples during long-term azithromycin therapy follow-up without relation to be on colymicin inhaled therapy.

When analyzing group 3 patients that alternate common microorganisms and *P.aeruginosa* without bronchial colonization we can observe how long-term azithromycin therapy eradicates common microorganisms during follow up and reduces too AECOPD, hospitalizations and days of hospital stay. However the small group size did not allow statistically significant differences.

The potential limitations of our study are the absence of a control group and the small number of patients included.

In conclusion, we have shown that long-term azithromycin, at a dosage of 500 mgr three times a week, is associated with a significant reduction of AECOPD, hospitalizations and days of mean hospital stay in patients with severe COPD and repeated AECOPD. This improvement is especially significant in patients with AECOPD for common microorganisms due to its antibacterial activity but also in those with chronic bronchial colonization by Pseudomonas aeruginosa providing important properties as an inmunomodulatiry agent and preventing AECOPD for common microorganisms. Long-term azithromycin may be reserved in severe COPD patients at high risk of exacerbations.

Bibliography:

1. **Seemungal, T.A., et al.,** ***Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease.*** **Am J Respir Crit Care Med, 1998. 157(5 Pt 1): p. 1418-22.**
2. **Soler-Cataluna, J.J., et al.,** ***Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease.*** **Thorax, 2005. 60(11): p. 925-31.**
3. **Moreno, A., et al.,** ***[Causes of death and risk factors for mortality in patients with severe chronic obstructive pulmonary disease].*** **Arch Bronconeumol, 2009. 45(4): p. 181-6.**
4. **Monso, E., et al.,** ***Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush.*** **Am J Respir Crit Care Med, 1995. 152(4 Pt 1): p. 1316-20.**
5. **Kunisaki, K.M. and D.E. Niewoehner,** ***Antibiotic prophylaxis for chronic obstructive pulmonary disease: resurrecting an old idea.*** **Am J Respir Crit Care Med, 2008. 178(11): p. 1098-9.**
6. **Kudoh, S., et al.,** ***Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin.*** **Am J Respir Crit Care Med, 1998. 157(6 Pt 1): p. 1829-32.**
7. **Southern, K.W., P.M. Barker, and A. Solis,** ***Macrolide antibiotics for cystic fibrosis.*** **Cochrane Database Syst Rev, 2004(2): p. CD002203.**
8. **Clement, A., et al.,** ***Long term effects of azithromycin in patients with cystic fibrosis: A double blind, placebo controlled trial.*** **Thorax, 2006. 61(10): p. 895-902.**
9. **Wolter, J., et al.,** ***Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial.*** **Thorax, 2002. 57(3): p. 212-6.**
10. **Saiman, L., et al.,** ***Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial.*** **Jama, 2003. 290(13): p. 1749-56.**
11. **Gan, W.Q., et al.,** ***Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis.*** **Thorax, 2004. 59(7): p. 574-80.**
12. **Suzuki, T., et al.,** ***Erythromycin and common cold in COPD.*** **Chest, 2001. 120(3): p. 730-3.**
13. **Seemungal, T.A., et al.,** ***Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations.*** **Am J Respir Crit Care Med, 2008. 178(11): p. 1139-47.**
14. **Rodriguez-Roisin, R.,** ***Toward a consensus definition for COPD exacerbations.*** **Chest, 2000. 117(5 Suppl 2): p. 398S-401S.**
15. **Pomares Amigo, X. and C. Monton Soler,** ***[Respiratory day hospital: What have we learned?].*** **Med Clin (Barc), 2009.**
16. **Vendrell, M., et al.,** ***[Diagnosis and treatment of bronchiectasis. Spanish Society of Pneumology and Thoracic Surgery].*** **Arch Bronconeumol, 2008. 44(11): p. 629-40.**

17. **Flume, P.A., et al., *Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health.* Am J Respir Crit Care Med, 2007. 176(10): p. 957-69.**
18. **Mensa, J., E. Garcia-Vazquez, and J. Vila, *[Macrolides, ketolides and streptogramins].* Enferm Infecc Microbiol Clin, 2003. 21(4): p. 200-7; quiz 208, 219.**
19. **Huang, B.H., et al., *Azithromycin-induced torsade de pointes.* Pacing Clin Electrophysiol, 2007. 30(12): p. 1579-82.**
20. **Martinez, F.J., J.L. Curtis, and R. Albert, *Role of macrolide therapy in chronic obstructive pulmonary disease.* Int J Chron Obstruct Pulmon Dis, 2008. 3(3): p. 331-50.**
21. **Shinkai, M., M.O. Henke, and B.K. Rubin, *Macrolide antibiotics as immunomodulatory medications: proposed mechanisms of action.* Pharmacol Ther, 2008. 117(3): p. 393-405.**
22. **Tagaya, E., et al., *Effect of a short course of clarithromycin therapy on sputum production in patients with chronic airway hypersecretion.* Chest, 2002. 122(1): p. 213-8.**
23. **Tamaoki, J., et al., *Effect of clarithromycin on sputum production and its rheological properties in chronic respiratory tract infections.* Antimicrob Agents Chemother, 1995. 39(8): p. 1688-90.**
24. **Parnham, M.J., et al., *Modulation of neutrophil and inflammation markers in chronic obstructive pulmonary disease by short-term azithromycin treatment.* Eur J Pharmacol, 2005. 517(1-2): p. 132-43.**
25. **Culic, O., et al., *Azithromycin modulates neutrophil function and circulating inflammatory mediators in healthy human subjects.* Eur J Pharmacol, 2002. 450(3): p. 277-289.**
26. **Garcia-Vidal, C., et al., *Pseudomonas aeruginosa in patients hospitalised for COPD exacerbation: a prospective study.* Eur Respir J, 2009. 34(5): p. 1072-8.**
27. **Miravitlles, M., et al., *Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD.* Chest, 1999. 116(1): p. 40-6.**
28. **Pauwels, R.A., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary.* Am J Respir Crit Care Med, 2001. 163(5): p. 1256-76.**
29. **Southern, K.W. and P.M. Barker, *Azithromycin for cystic fibrosis.* Eur Respir J, 2004. 24(5): p. 834-8.**
30. **Tateda, K., et al., *Suppression of Pseudomonas aeruginosa quorum-sensing systems by macrolides: a promising strategy or an oriental mystery?* J Infect Chemother, 2007. 13(6): p. 357-67.**
31. **Baumann, U., et al., *Buccal adherence of Pseudomonas aeruginosa in patients with cystic fibrosis under long-term therapy with azithromycin.* Infection, 2001. 29(1): p. 7-11.**