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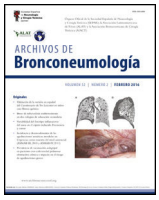

Special article

Consensus document on the diagnosis and treatment of chronic bronchial infection in chronic obstructive pulmonary disease☆

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ABSTRACT

Although the chronic presence of microorganisms in the airways of patients with stable chronic obstructive pulmonary disease (COPD) confers a poor outcome, no recommendations have been established in disease management guidelines on how to diagnose and treat these cases.

In order to guide professionals, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) has prepared a document which aims to answer questions on the clinical management of COPD patients in whom microorganisms are occasionally or habitually isolated. Since the available scientific evidence is too heterogeneous to use in the creation of a clinical practice guideline, we have drawn up a document based on existing scientific literature and clinical experience, addressing the definition of different clinical situations and their diagnosis and management. The text was drawn up by consensus and approved by a large group of respiratory medicine experts with extensive clinical and scientific experience in the field, and has been endorsed by the SEPAR Scientific Committee.

Documento de consenso sobre el diagnóstico y tratamiento de la infección bronquial crónica en la enfermedad pulmonar obstructiva crónica

Palabras clave:
Enfermedad pulmonar obstructiva crónica
Infección bronquial crónica
Bronquiectasias
Tratamiento antibiótico inhalado
Macrólidos
Corticosteroides inhalados

RESUMEN

A pesar de que es conocido que la presencia crónica de microorganismos en las vías aéreas de pacientes con enfermedad pulmonar obstructiva crónica (EPOC) en fase de estabilidad conlleva una evolución desfavorable, ninguna guía de manejo de la enfermedad establece pautas sobre cómo diagnosticar y tratar este tipo de casos.

Con la intención de orientar a los profesionales, desde la Sociedad Española de Neumología y Cirugía Torácica (SEPAR) se ha elaborado un documento que pretende aportar respuestas clínicas sobre el manejo

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de pacientes con EPOC en los que se aíslan microorganismos de forma puntual o persistente. Dado que la heterogeneidad de las evidencias científicas disponibles no permite crear una Guía de Práctica Clínica, se ha elaborado un documento basado en la literatura científica existente y/o en la propia experiencia clínica que aborda tanto la definición de las diferentes situaciones clínicas como su diagnóstico y manejo. El texto ha sido consensuado entre un amplio número de neumólogos con gran experiencia clínica y científica en este ámbito. Este documento cuenta con el aval del Comité Científico de SEPAR.

Introduction

Chronic obstructive pulmonary disease (COPD) presents with chronic bronchial inflammation that alters local defense mechanisms, meaning that potentially pathogenic microorganisms (PPMs) are isolated from respiratory sample cultures of 8%-43% of patients in a clinically stable phase.[1,2] These isolates are more frequent in more severe cases, exacerbators, and patients with chronic bronchitis, bronchiectasis, and low peripheral eosinophil counts.[3–6] Table 1 lists the most common PPMs.

The presence of PPMs in clinically stable patients has several consequences, such as increased bronchial neutrophil inflammation,[3,7–11] increased sputum purulence,[10,12] progressive FEV_1 decline,[8,13–15] worse quality of life,[16,17] more frequent and more severe exacerbations,[11,18,19] and higher mortality,[20,21] probably due to low-grade infection that can contribute to the progression of COPD.[22]

The methodologies of the scientific evidence in this area vary widely and generate controversy around the definition, diagnosis, and management of these patients, so COPD treatment guidelines provide few recommendations in this regard.[23,24] However, the presence of PPMs may have therapeutic implications, and may affect the use of certain treatments such as inhaled corticosteroids (ICS) or antibiotic therapy. In order to guide clinicians, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) has prepared a consensus document based on the scant scientific literature available and the experience of experts. This document only addresses the diagnosis and management of COPD patients in whom PPMs are isolated from respiratory samples.

The methodology for the preparation of this document is detailed in Appendix B Online Supplement 1.

Module 1. Definitions

Given the poor sensitivity of sputum culture results and the limited microbiological monitoring that is usually carried out, it is difficult to prove the microbiological status of the COPD patient. No validated definitions are available for the presence of PPMs in the airway in these individuals, so the following definitions were agreed upon:

- *Primary infection:* The first isolation of a given PPM in a respiratory sample culture from a patient in a clinically stable disease stage.
- *Chronic bronchial infection* (CBI): Growth of the same PPM in at least 3 cultures in a period of 1 year, performed at least 1 month apart.
- *Eradication*: When the PPM causing the CBI is not isolated in at least 3 consecutive cultures in a 1-year period, performed at least 1 month apart.
- If a PPM is isolated again after eradication, it will be considered as another primary infection, provided the patient is not receiving chronic antibiotic therapy.
- For patients who do not exactly meet these definitions, the case should be classified as the closest in clinical terms.

Fig. 1 shows a summary of the management of COPD patients with exceptional or persistent PPM isolates.

Module 2. Microbiological aspects

Despite their limitations, standard culture techniques are still used for the isolation of PPMs in respiratory samples,[25] since molecular techniques, albeit useful in the determination and study of the pulmonary microbiota,[26,27] are costly.[28,29]

A special case is that of *Pseudomonas aeruginosa*, present in 3% to 20% of stable patients with certain risk factors: FEV_1 < 50%, more than 3 exacerbations in the previous year, chronic use of oral corticosteroids, bronchiectasis, admission to intensive care, and a high BODE index.[5,30–33] It confers a more severe COPD phenotype than other PPMs, with more inflammation,[34] exacerbations, and mortality.[19,35–37]

In the case of other microorganisms, isolation of *Aspergillus* is common in patients with certain risk factors, and is associated with more symptoms.[38,39] Detection rates of non-tuberculous mycobacteria have increased in the past 10 years[40]: these microorganisms are associated with more frequent COPD exacerbations and accelerated functional decline.[41]

Agreement was reached on the following recommendations for the microbiological diagnosis and follow-up of COPD patients:

- Perform sputum culture as part of the initial study in high-risk COPD23 and/or in the case of persistent mucopurulent expectoration.
- Samples with > 25 leukocytes and < 25 epithelial cells per field (Murray-Washington grades 4–5) are valid.[42] In case of non-valid samples, sampling should be repeated (especially if there is high suspicion of CBI or if *P. aeruginosa* has been isolated).
- Perform microbiological follow-up on all patients with previous PPM isolated in a clinically stable phase or with 1 of the criteria listed in Table 2.[18,43–45]
- Monitor sputum color, as this is associated with the presence of PPM in stable COPD[46,47] (Fig. 2).
- Cultures for fungi and/or non-tuberculous mycobacteria should be performed at least once a year, even if the patient is stable. This should also be performed in patients with: ≥ 2 exacerbations requiring systemic steroids and/or antibiotics in the last year; treatment with high-dose ICS; bronchiectasis; if radiological images are compatible with mycobacterial infection; before and during chronic macrolide treatment (for mycobacteria); and if there is no clinical improvement despite proper treatment of isolated PPMs.[38–41,48–50]
- In cases where a microorganism considered not potentially pathogenic ("mixed oropharyngeal flora" or "normal flora") is isolated, no further action is necessary, unless there is a high suspicion of CBI.
- Time between collection, transport and processing of the samples must be less than 6 h. In any case, samples should not remain more than 24 h at room temperature, and should preferably be stored at 4°C rather than −20°C.[51]

Table 1
List of the most frequently isolated microorganisms in COPD patients[128–131].

PPM	Non-PPM
Haemophilus influenzae *Streptococcus pneumoniae* *Moraxella catarrhalis* *Pseudomonas aeruginosa* Other non-fermenting gram-negative bacilli (*Achromobacter xylosoxidans*, *Acinetobacter baumannii*, *Alcaligenes faecalis*, *Stenotrophomonas maltophilia*, *Pseudomonas* spp., . . .) *Klebsiella pneumoniae* Other *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella aerogenes*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus* spp., *Povidencia* spp., *Citrobacter* spp. . . .) *S. aureus*, including MRSA *Pasteurella multocida*	*Streptococcus* of the *viridans* group *Gemella morbillorum* *Neisseria* commensals *Staphylococcus epidermidis* and other CoNS *Micrococcus* spp. *Enterococcus* spp.

CoNS: coagulase-negative staph; MRSA: methicillin-resistant *Staphylococcus aureus*; non-PPM: non-potentially pathogenic microorganisms or usual flora; PPM: potentially pathogenic microorganisms.

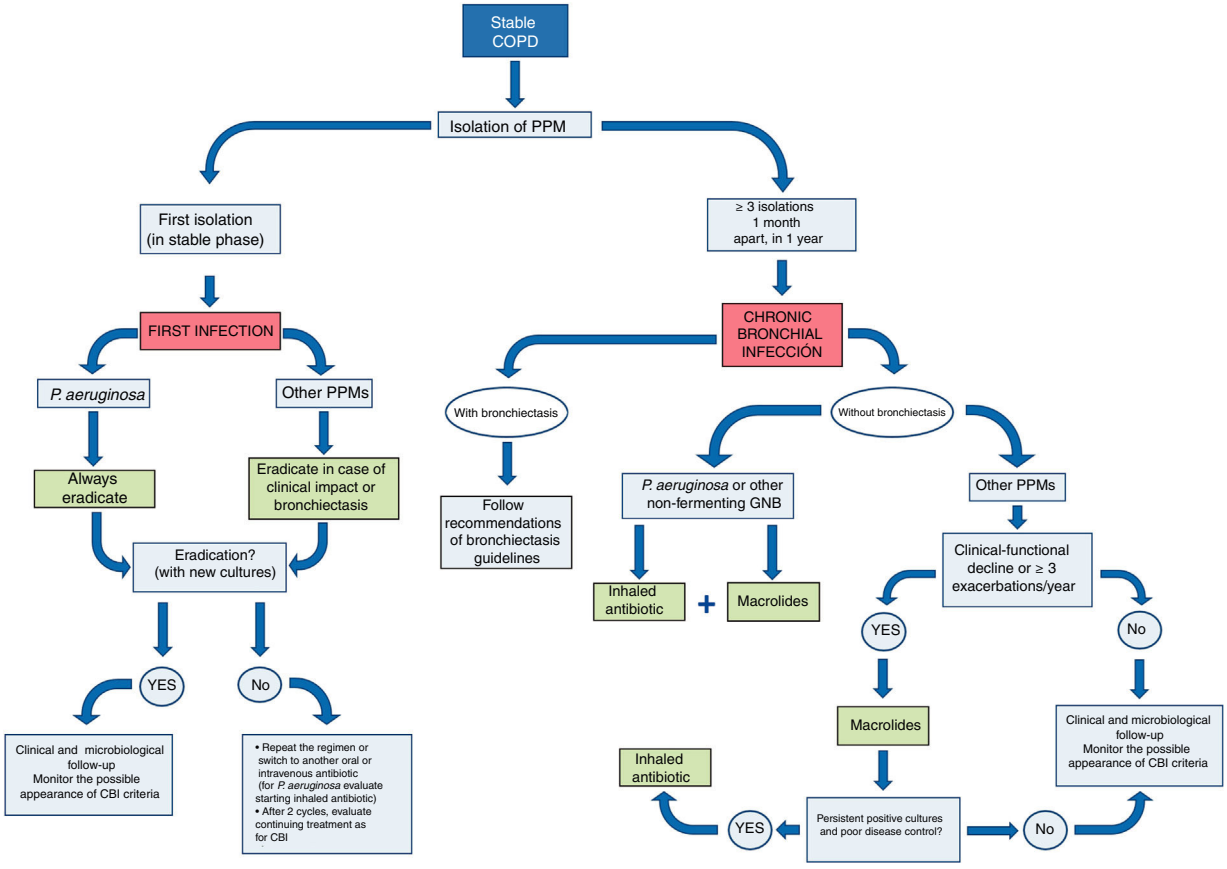

Fig. 1. Summary of management of COPD patients in whom potentially pathogenic microorganisms are isolated.
GNB: gram-negative bacilli; COPD: chronic obstructive pulmonary disease; CBI: chronic bronchial infection; PPM: potentially pathogenic microorganisms.

Table 2
Clinical criteria for deciding on the treatment of primary PPM infection other than *P. aeruginosa* in clinically stable patients with COPD (at least one must be met)[a].

Persistent mucopurulent/purulent (Murray scale 3–8) or hemoptoic expectoration
Poor disease control[132,133]: increased dyspnea, increased need for rescue medication, decreased physical activity, increased sputum purulence, CAT score decline
Progressive worsening of lung function
Frequent infectious exacerbations (≥ 2 exacerbations requiring oral antibiotic treatment or ≥ 1 requiring hospitalization or intravenous antibiotic treatment)

CBI: chronic bronchial infection; COPD: chronic obstructive pulmonary disease; PPM: potentially pathogenic microorganisms.
[a] To be evaluable, all these criteria must be present in a patient receiving optimal treatment at the discretion of the treating physician, including drug prescription, verification of the inhalation technique, and compliance.

Module 3. Relationship between COPD, chronic bronchial infection, and the presence of bronchiectasis

CBI may contribute to the appearance and/or progression of bronchiectasis in COPD patients.[52] Bronchiectasis is associated with more severe and symptomatic forms of COPD: increased sputum production and purulence, more comorbidities, greater dyspnea, greater bronchial obstruction, more frequent and severe exacerbations, increased bacterial burden, increased risk

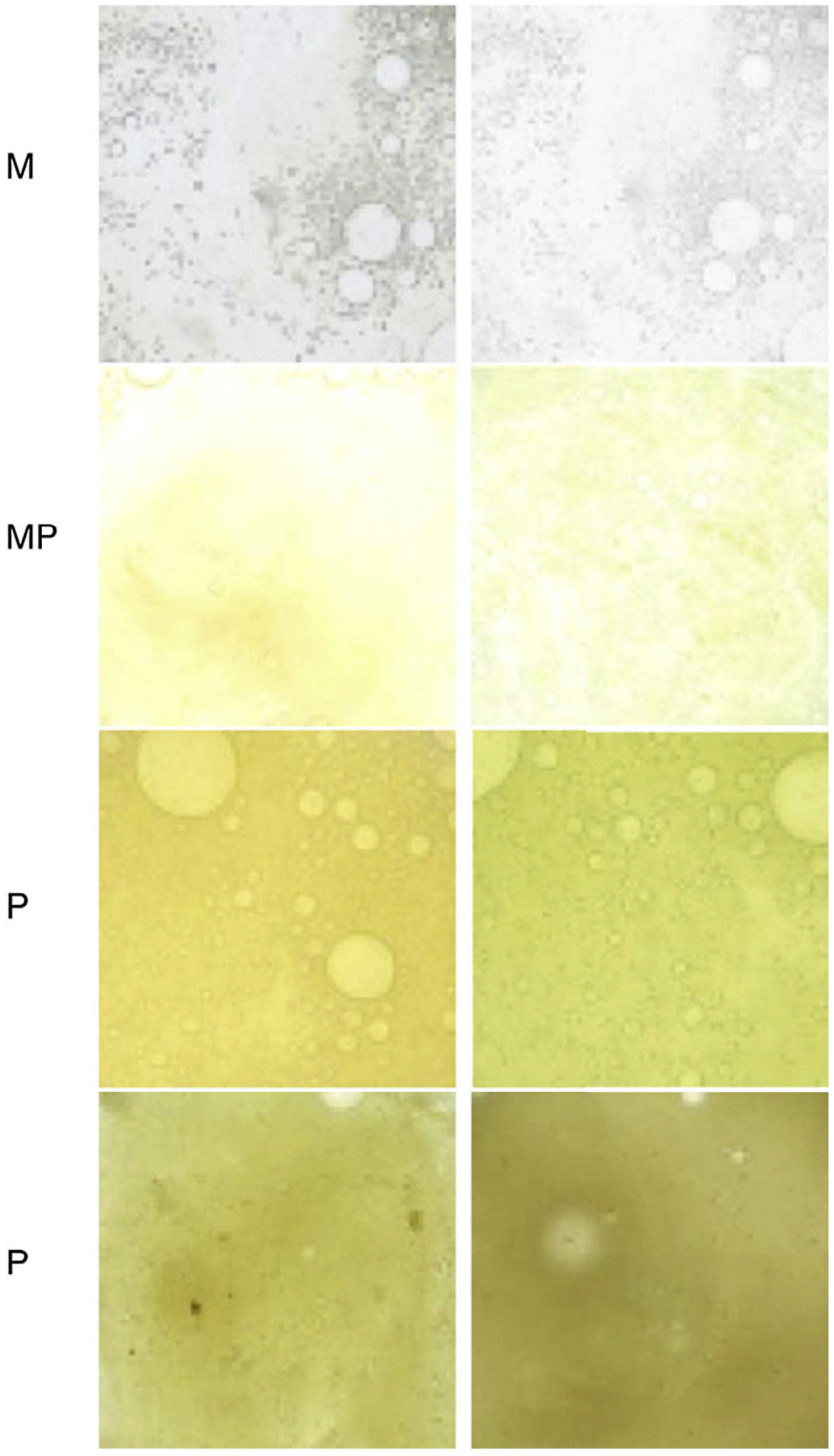

Fig. 2. Murray scale to assess sputum color from lowest to highest purulence. M: mucoid; MP: mucopurulent; P: purulent.
Source: Reproduced with permission from Murray et al.[47]

of CBI (particularly due to *P aeruginosa*) and increased risk of mortality.[44,45,53–59] Therefore, detection of bronchiectasis is important, since the patient may benefit from specific treatments.[60] In these patients, antibiotic treatment is essential, because while eradication is virtually impossible, it reduces bacterial counts, decreases exacerbations, and improves lung function.[61] There is no evidence that the presence of bronchiectasis increases the likelihood of isolating microorganisms that are resistant to standard antibiotics.[62]

Agreement was reached on the following statements on the relationship between COPD, CBI, and bronchiectasis:

- A high-resolution computed tomography scan of the chest should be performed to assess the presence of bronchiectasis in patients with certain clinical characteristics (Table 3).[51]
- If COPD and bronchiectasis co-exist in the patient, follow the definitions and therapeutic regimens proposed by the bronchiectasis

Table 3
Clinical criteria that warrant a high-resolution computed tomography scan of the chest in patients with COPD to assess the presence of bronchiectasis.

High-risk COPD[23]
Frequent infectious exacerbations (≥ 2 exacerbations requiring oral antibiotic treatment or ≥ 1 requiring hospitalization or intravenous antibiotic treatment)
Persistent mucopurulent or purulent expectoration
Hemoptoic expectoration
X-ray changes suggestive of bronchiectasis
Repeated isolation of PPM (or a single isolation of *P. aeruginosa*)
Progressive functional decline
Presence of comorbidities associated with the development of bronchiectasis[51]

PPM: Potentially pathogenic microorganisms.

guidelines with regard to the isolation of PPMs in cultures of respiratory samples.[51]
- These patients should be managed according to the treatment guidelines for both COPD[23,24] and bronchiectasis.[63–65]

Module 4. Treatment of primary infection

In COPD patients without bronchiectasis, there is no evidence to indicate the best eradication strategy or whether primary infection should be treated. However, *P. aeruginosa*, particularly mucoid strains,[66] is liable to persist and, like *Haemophilus influenzae*, it has a tendency to form biofilms that hinder the action of antimicrobials and promote the persistence of the microorganism.[67–70]

Agreement was reached on the following recommendations for the treatment of primary infection (Fig. 1):

- In primary infection with *P. aeruginosa*, eradication treatment is always advisable.
- For other PPMs, consider eradication therapy in stable patients with bronchiectasis or at least 1 of the criteria listed in Table 2.
- Table 4 shows the most common PPM eradication treatment regimens.
- It is advisable to verify eradication with sputum cultures at least 15 days after the end of treatment. If eradication is not achieved after 2 cycles, consider treating as CBI (Table 4).

Module 5. Inhaled antibiotic therapy

The use of inhaled antibiotic (IA) therapy has increased remarkably due to its good results in the treatment of CBI in cystic fibrosis[71] and bronchiectasis.[72] IAs achieve high concentrations in the bronchial tree and produce few systemic adverse effects.[73,74] There are no published clinical trials in COPD, but some small studies with colistin, tobramycin, and amoxicillin-clavulanic acid have reported good outcomes and few adverse effects.[75–79]

Agreement was reached on the following recommendations for IA treatment in patients with COPD and CBI (Fig. 1 and Table 4). In all cases, it should be confirmed that the patient is receiving correct treatment for COPD (including correct prescription, inhalation technique, and adherence).

- If COPD and bronchiectasis co-exist, follow bronchiectasis guidelines on the treatment of CBI with IA.[63]
- Prescribe IAs in patients with CBI caused by *P. aeruginosa* or other particularly virulent non-fermenting gram-negative bacilli (Table 1).
- Treat patients with CBI caused by other PPMs, with clinical and functional deterioration or frequent infectious exacerbations, with long-term macrolides.[23,80] If positive cultures and poor disease control persist, start IA.
- The decision to prescribe a specific IA depends on the PPMs rather than on the susceptibility testing results, since IAs reach far higher levels in bronchial mucosa than the mean inhibitory concentration. An IA to which the PPM family is known to be susceptible must be selected.
- The dosage is the same as that used in bronchiectasis (Table 5).
- Maintain IA treatment as long as a clinical benefit is observed, i.e., the least purulent sputum possible according to the sputum color scale in Fig. 2 and reduction of exacerbations. Assess withdrawal after 6 months in case of clinical stability and negative cultures. In this case, continue with close microbiological monitoring, and if CBI reappears, give long-term treatment.
- Given the possible risk of allergy, bronchospasm, dyspnea, cough or hemoptysis,[81–83] take certain precautions when using IAs, especially in patients with more severe COPD:

none- Education on the use and maintenance of devices.
none- Pre-inhalation of fast-acting bronchodilators.
none- Administer the first dose in the hospital setting, either in a day hospital (with observation for 2–3 hours) or during a short hospital stay (in the most severe patients).
none- In severe COPD, consider the risk of IA-induced bronchoconstriction. Assess the possibility of performing spirometry before and after the first dose (reduction of $FEV_1 \geq 15\%$).[84] If bronchoconstriction is observed, consider changing the type of IA, the diluent or the volume of nebulization.

- Assess the risk of nephrotoxicity and ototoxicity due to aminoglycosides: avoid their use in severe chronic renal insufficiency; perform 6-monthly analytical testing during the first year (then annual); evaluate hearing loss during treatment.[85]
- If the patient performs bronchial drainage techniques or receives nebulized hypertonic saline therapy, these should precede IA.

Module 6. Long-term macrolide treatment

Macrolides (the most widely studied is azithromycin) modulate neutrophilic bronchial inflammation, interfere with biofilm formation, reduce bacterial load, and reduce exacerbations.[86–89] Although the emergence of resistance is a possible long-term risk,[90,91] the benefits of this treatment are currently thought to outweigh the risks.[23,24,90,92]

Agreement was reached on the following recommendations for macrolide treatment in patients with COPD and CBI (Fig. 1):

- Start macrolide treatment in stable patients with 3 or more exacerbations/year (moderate or severe, requiring antibiotic treatment), despite the correct core treatment.
- In the case of CBI due to *P. aeruginosa*, monotherapy with macrolides is inadvisable; instead, these compounds should be combined with IA.
- The regimens supported by the most evidence are: azithromycin 500 mg/day, 3 days/week, or azithromycin 250 mg daily, for 1 year. Treatment will subsequently be individualized according to clinical response (reduction of exacerbations and expectoration) and the appearance of side effects.
- Due to the seasonal distribution of exacerbations,[93] a treatment holiday may be considered during the warm months, if there has been a long period of stability without exacerbations and little mucous secretion. Consider restarting in autumn (or before, if exacerbations reappear).
- Electrocardiogram, liver function tests, mycobacterial culture, and hearing evaluation should be performed before starting treatment. Assess whether to repeat these tests at least annually in

Table 4
Recommendations for antibiotic treatment in COPD patients without bronchiectasis, with PPM isolated from respiratory samples.

	P. aeruginosa	H. influenzae	S. aureus	MRSA	Non-fermenting GNB other than *P. aeruginosa*
Treatment of primary infection	First option: Ciprofloxacin 750 mg/12 h p.o. Alternative: Levofloxacin 500 mg/12 h p.o. or 750 mg/24 h p.o. Duration 2–3 weeks (based on clinical improvement and tolerance)	First option: Amoxicillin/clavulanic acid 875/125 mg/8 p.o. Alternatives: Amoxicillin 1–2 g/8 h p.o. Ciprofloxacin 750 mg/12 h p.o. Azithromycin 500 mg/24 h p.o. Cefditoren 400 mg/12 h p.o. Duration 10–14 days except azithromycin (6 days) and cefditoren (10 days)	First option: Cloxacillin 500–1,000 mg/6 h p.o. Alternatives: Amoxicillin/clavulanic acid 875 mg/8 h p.o.. Cotrimoxazole 160/800 mg/12 h p.o. Duration 2 weeks	First option: Linezolid 600 mg/12 h p.o. Alternatives: Cotrimoxazole 160/800 mg/12 h p.o. Clindamycin 300–450 mg/6–8 h p.o. Duration 2 weeks	S. maltophilia: First option: Cotrimoxazole 800/160 mg/12 h p.o. Alternative: Levofloxacin 500 mg/12 h p.o. A. baumani • Imipenem 0.5–1 g/6–8 h i.v. Duration 2 weeks
If not eradicated after a first treatment cycle	Repeat the regimen Assess i.v. treatment Assess inhaled antibiotic therapy	Repeat the regimen or switch to another antibiotic (p.o. or i.v.)	Repeat the regimen or switch to another antibiotic (p.o. or i.v.)	Repeat the regimen or switch to another antibiotic (p.o. or i.v.)	S. maltophilia: • Minocycline 200 mg loading dose, 100 mg/12 h p.o. or i.v. • Colistin: 2–3 MU/8 h or 4.5 MU/12 h i.v. A. baumani • Tigecycline: 100 mg loading dose, 50 mg/12 h i.v. • Colistin 2–3 MU/8 h or 4.5 MU/12 h i.v.
Treatment of severe exacerbation (or first isolation detected during severe exacerbation)	First option: Ceftazidime 2 g/8 h p.o. + Tobramycin 5–10 mg/kg/24 h i.v. Alternatives: Imipenem 1 g/8 h i.v. or Piperacillin/tazobactam 4 g/6–8 h i.v. or Aztreonam 2 g/8 h i.v. or Cefepime 1–2 g/8 h i.v. or Meropenem 2 g/8 h i.v. or Ciprofloxacin 400 mg/12 h i.v. or Ceftolozane/tazobactam 1–2 g/8 h i.v. or Ceftazidime-avibactam 3 g/8 h i.v. + Amikacin 15–20 mg/kg/24 h i.v. or Gentamicin 5–7 mg/kg/24 h i.v. Duration 14–21 days (based on clinical improvement)	First option: Amoxicillin/clavulanic acid 1–2 g/8 h i.v. Alternative: Ceftriaxone 2 g/24 h i.v. Duration 10–14 days (start antibiotic treatment i.v. and switch to p.o. when permitted by the patient's clinical situation)	First option: Cloxacillin 1–2 g/4–6 h i.v. Alternatives: Amoxicillin/clavulanic acid 1–2 g/8 h i.v. Vancomycin (dose adjusted for weight and renal function) Duration 2 weeks	First option: Linezolid 600 mg/12 h i.v. Alternatives: Vancomycin (dose adjusted for weight and renal function) Ceftaroline 600 mg/8 h i.v. Ceftobiprole medocaril 500 mg/8 h i.v. Duration 2 weeks	S. maltophilia: First option: Cotrimoxazole 800/160 mg/12 h i.v. Alternative: Levofloxacin 500 mg/12 h i.v. A. baumani • Imipenem 0.5–1 g/6–8 h i.v. Duration 2 weeks
Treatment of CBI	Start inhaled antibiotic therapy with (in alphabetical order): • Aztreonam lysine (inhalation solution) • Gentamycin (i.v. formulation administered by inhaled route) • Sodium cholistimethate (dry powder or inhalation solution) • Tobramycin (dry powder or inhalation solution) Combine with long-term macrolides	1. Long-term macrolide treatment 2. If not effective, start long-term (or cyclic) oral antibiotic treatment, according to susceptibility testing 3. If not effective, start inhaled antibiotics with gentamicin (80 mg, twice a day, continuous treatment) or any of the specific inhalation antibiotics used in CBI caused by *P. aeruginosa*	1. Long-term macrolide treatment 2. If not effective, start long-term (or cyclic) oral antibiotic treatment, according to susceptibility testing 3. If not effective, start inhaled antibiotics with gentamicin (80 mg, twice a day, continuous treatment) or any of the specific inhalation antibiotics used in CBI caused by *P. aeruginosa*	1. Long-term macrolide treatment 2. If not effective, start long-term (or cyclic) oral antibiotic treatment, according to susceptibility testing 3. If not effective, start vancomycin inhaled antibiotic therapy (IV formulation administered by inhaled route), continuous treatment, 250 mg, twice a day	Start inhaled antibiotic therapy with sodium cholistimethate (dry powder or inhalation solution) Combine with long-term macrolides

CBI: Chronic bronchial infection; IV: intravenous; v.o.: oral route; MRSA: methicillin-resistant *S. aureus*.

Table 5
Antibiotics specifically designed for inhalation available on the market[a].

	Dosis, regimen	Administration time	Inhalation system
Aztreonam lysine, inhalation solution	75 mg, 3 times daily, on/off[b]	2–3 min	E-Flow® nebulizer system (Altera)
Colistimethate, dry powder for inhalation	1,662,500 IU, twice daily, continuous treatment	1–2 min	Turbospin®
Colistimethate, solution for inhalation	1–2 million IU, twice daily, continuous treatment	Variable, depending on the nebulizer	E-Flow® nebulizer system, Pari LC plus®
	0.5–1 million IU, twice daily, continuous treatment	3–6 min	I-neb AAD®
Tobramycin, dry powder for inhalation	112 mg, 2 times daily, on/off[b]	~ 6 min	T-326 inhaler
Tobramycin, solution for inhalation	300 mg/5 mL, twice a day on/off[b]	Variable, depending on the nebulizer	E-Flow® nebulizer system, Pari LC plus®
	300 mg/4 mL, twice a day on/off[b]	Variable, depending on the nebulizer	

[a] In exceptional cases, depending on the type of potentially pathogenic microorganism or its susceptibility to antibiotics, parenteral formulations of some antibiotics may be administered by the nebulized route: gentamycin (80 mg/12 h continuously), vancomycin (250 mg/12 h continuously) or ceftazidime (1 g/12 h continuously).
[b] On/off cycles are 28 days.

prolonged treatments. Appendix B Online Supplement 2 details the requirements and precautions to be taken when initiating long-term macrolide treatment.

Module 7. Inhaled corticosteroid therapy

ICS therapy reduces exacerbations and improves symptoms and quality of life in patients with advanced COPD.[94] ICS in patients with COPD, frequent bacterial exacerbations, CBI, and/or low blood eosinophils are associated with adverse effects: these compounds alter the antiviral immune response,[95] modify the composition of the microbiome,[96] and increase the bacterial load[97] and the risk of upper airway infections, pneumonia[98–100] and non-tuberculous mycobacteria.[101,102]

Agreement was reached on the following recommendations for ICS treatment in patients with COPD and CBI:

- Special precautions must be taken with the use of ICS in patients with CBI63.
- If they are prescribed, consider using the lowest possible dose.
- Re-evaluate the risk/benefit ratio of ICS use in patients who do not present: eosinophilia (persistently < 100 eosinophils/mm^3) or features consistent with concomitant asthma.[23]

Module 8. Other maintenance treatments

Respiratory rehabilitation and physiotherapy programs are underutilized, despite showing improvement in various health outcomes, including bronchial symptoms, respiratory function, quality of life, and risk of hospital readmission.[103,104] Physical activity programs should be an integral and complementary part of respiratory rehabilitation, as they improve physical fitness and promote a healthier lifestyle in COPD patients.[105]

Prolonged use of mucolytics in COPD may have clinical benefits in exacerbators, especially N-acetyl cysteine and carbocysteine.[93,106–109]

Given the increased risk of malnutrition and increased energy requirement of COPD patients, adequate nutritional assessment, diet and nutrition are essential.[110–112]

The use of probiotics appears to reduce the rate of upper respiratory tract infections,[113] and their potential effect also seems promising in lung infections.[114] They can also help prevent diarrhea and antibiotic-induced dysbiosis.[115–117]

Agreement was reached on the following recommendations for other treatments in patients with COPD and CBI:

- A respiratory rehabilitation program (including health education, respiratory physiotherapy, muscle training, and physical activity programs) should be prescribed for patients with persistent expectoration, dyspnea grade ≥ 2, or low physical activity levels.
- Prolonged treatment with N-acetyl cysteine or carbocysteine may be considered in COPD patients with frequent exacerbations23,24.
- A nutritional assessment should be made in patients with COPD and CBI, including at least: body mass index, nutritional intake, and a longitudinal evaluation of progressive weight loss.
- Assess, according to the physician's criteria, the possible benefit of the use of probiotics in patients who require several antibiotic cycles per year, coinciding with each cycle, in order to avoid diarrhea and intestinal dysbiosis.

Module 9. Management of exacerbations in patients with COPD and chronic bronchial infection

COPD exacerbations have a very varied etiology. Bacterial etiology is usually mediated by an increase in the bronchial bacterial load,[118] the acquisition of new strains of a specific bacterium,[119,120] or changes in the bronchial microbiome.[121] However, evidence suggests that PPMs colonizing the lower airway during the stable phase are associated with PPMs isolated during exacerbations.[122]

Agreement was reached on the following recommendations for the management of exacerbations in patients with COPD and CBI:

- A sputum sample for culture should always be collected at the beginning of the exacerbation before starting antibiotic treatment.
- A previous CBI should guide the choice of antibiotic according to the results of the last susceptibility testing (anticipated treatment) and the antibiotic susceptibility data of the hospital (Table 4).
- Adjust treatment if the result of the new culture is different from the previous one or if the clinical course of the exacerbation is unfavorable.
- If during an exacerbation a different PPM is isolated from that which is causing the CBI, administer antibiotic treatment covering both PPMs (Table 4)[9,15,121–128]
- In general, any exacerbation of COPD should assess risk factors for *P. aeruginosa* being involved.
- After an exacerbation involving a PPM, a follow-up culture should be performed at least 15 days after the end of antibiotic treatment whenever possible.

Table 6
Information to be recorded during follow-up visits in patients with COPD and chronic bronchial infection. Additional scans recommended.

	At each visit	Yearly	Exacerbations	Other times
Clinical data				
Signs and symptoms in stable phase:				
Dyspnea (mMRC scale)				
Clinical criteria for chronic bronchitis				
Volume (semi-quantitative marked in a graduated vessel); color (Murray scale[47])				
Symptoms suggestive of asthma/bronchial hyperreactivity				
Hemoptoic expectoration				
Systemic symptoms (fever, weight loss, etc.)				
$SatO_2$				
Exacerbations:				
Number of exacerbations with antibiotics and/or corticosteroids				
Number of admissions for exacerbation or home intravenous antibiotic treatment				
Impact of the disease:				
Quality of life: CAT questionnaire[134]				
Severity: BODEx score[135]				
Treatments				
Pharmacological treatment				Seasonal influenza vaccination
Smoking habit				Pneumococcal vaccination (preferably 13-valent conjugate) once in lifetime
Exercise and physical activity				
Physiotherapy				
Influenza and pneumococcal vaccination				
Pharmacological treatment				
Compliance				
Adverse effects				
Inhalation technique				
Satisfaction with inhalation devices				
Laboratory / microbiology				
Sputum culture				Also request culture of fungi and/or mycobacteria once a year, or suspected on clinical/radiological examination, and before/during long-term macrolide treatment (see Module 2)
Clinical laboratory testing[a]				At diagnosis of CBI At the start of chronic treatment with macrolides or inhaled antibiotics; in the case of inhaled aminoglycosides, perform every 6 months
Respiratory function tests				
Forced spirometry				
6-minute walk test				In case of clinical, functional and/or deterioration of $SatO_2$
Plethysmography/diffusion				According to clinical symptoms and availability
Imaging tests				
Chest X-ray				
High-resolution computed tomography				At diagnosis of CBI (to assess possible associated bronchiectasis) Every 2 years in case of rapid clinical-functional deterioration, frequent hemoptysis or risk factors for poor progression For all other patients every 4–5 years[63]
Other complementary examinations				
Electrocardiogram				At diagnosis of CBI; before starting long-term azithromycin treatment
Evaluate hearing ± audiometry				Before starting and during long-term azithromycin treatment Perform audiometry in case of hearing loss during treatment

CAT: *COPD assessment test*; CBI: chronic bronchial infection; mMRC: modified Medical Research Council.
[a] Assessment of inflammatory markers (C-reactive protein), alfa-1-antitrypsin,[136] eosinophilia, nutritional parameters (albumin) or adverse effects of treatment (renal, hepatic function, etc.).

Module 10. Follow-up of patients with COPD and chronic bronchial infection

Agreement was reached on the following recommendations for the follow-up of patients with COPD and CBI (Table 6):

- The initial follow-up after primary infection is determined by the need for microbiological monitoring (to assess eradication, reduction of bacterial load, or new PPMs) and clinical monitoring (reduction of symptoms and exacerbations).
- Schedule follow-up visits scheduled depending on COPD severity, the frequency of exacerbations, and functional progress. In severe patients (GOLD D, FEV1 < 50% and/or chronic respiratory failure), monitoring may be required at least every 3 months; in milder or more stable patients, visits may be performed every 4–6 months.

Table 7
Summary of clinical recommendations for the management of COPD patients in whom potentially pathogenic microorganisms are isolated. The degree of consensus reached by the Scientific Committee is specified for each recommendation (% of reviewers who have scored each score from 1 to 5 on the Likert scale).

	Disagree (score 1 or 2)	Indifferent (score 3)	Agree (score 4 or 5)
Module 1. Definitions			
Primary infection: The first isolation of a given PPM in a respiratory sample culture from a patient in a clinically stable disease stage	2.9	2.9	94.2
Chronic bronchial infection (CBI): Growth of the same PPM in at least 3 cultures in a period of 1 year, performed at least 1 month apart	↓	2.9	97.1
Eradication: When the PPM causing the CBI is not isolated in at least 3 consecutive cultures in a 1-year period, performed at least 1 month apart	2.9	↓	97.1
If a PPM is isolated again after eradication, it will be considered as another primary infection, provided the patient is not receiving chronic antibiotic treatment	↓	2.9	97.1
For patients who do not exactly meet these definitions, the case should be classified as the closest in clinical terms	↓	8.6	91.4
Module 2. Microbiological aspects			
Perform sputum culture as part of the initial study in high-risk COPD and/or in the case of persistent mucopurulent expectoration	↓	↓	100
Samples with > 25 leukocytes and < 25 epithelial cells per field (Murray-Washington grades 4–5) are valid. In case of non-valid samples, sampling should be repeated (especially if there is high suspicion of CBI or if *P. aeruginosa* has been isolated	↓	5.8	94.2
Perform microbiological follow-up on all patients with previous PPM isolated in a clinically stable phase or with 1 of the criteria listed in Table 2	↓	↓	100
Monitor sputum color, as this is associated with the presence of PPM in stable COPD (Fig. 2)	↓	2.9	97.1
Cultures for fungi and/or non-tuberculous mycobacteria should be performed at least once a year, even if the patient is stable. This should also be performed in patients with: ≥ 2 exacerbations requiring systemic steroids and/or antibiotics in the last year; treatment with high-dose ICS; bronchiectasis; if radiological images are compatible with mycobacterial infection; before and during chronic macrolide treatment (for mycobacteria); and if there is no clinical improvement despite proper treatment of isolated PPMs	↓	2.9	97.1
In cases where a microorganism considered not potentially pathogenic ("mixed oropharyngeal flora" or "normal flora") is isolated, no further action is necessary, unless there is a high suspicion of CBI	↓	2.9	97.1
Time between collection, transport and processing of the samples must be less than 6 h. In any case, samples should not remain more than 24 h at room temperature, and should preferably be stored at 4 °C rather than 20— °C.	↓	2.9	97.1
Module 3. Relationship between COPD, chronic bronchial infection, and the presence of bronchiectasis			
A high-resolution computed tomography scan of the chest should be performed to assess the presence of bronchiectasis in patients with certain clinical characteristics (Table 3)	↓	↓	100
If COPD and bronchiectasis co-exist in the patient, follow the definitions and therapeutic regimens proposed by the bronchiectasis guidelines with regard to the isolation of PPMs in cultures of respiratory samples	↓	5.8	94.2
These patients should be managed according to the treatment guidelines for both COPD and bronchiectasis	↓	2.9	97.1
Module 4. Treatment of primary infection			
In primary infection with *P. aeruginosa*, eradication treatment is always advisable	↓	2.9	97.1
For other PPMs, consider eradication therapy in stable patients with bronchiectasis or at least 1 of the criteria in Table 2	↓	2.9	97.1
Table 4 shows the most common PPM eradication treatment regimens	↓	↓	100
It is advisable to verify eradication with sputum cultures at least 15 days after the end of treatment. If eradication is not achieved after 2 cycles, consider treating as CBI (Table 4)	↓	↓	100
Module 5. Inhaled antibiotic therapy			
If COPD and bronchiectasis co-exist, follow bronchiectasis guidelines on the treatment of CBI with IA	2.9	↓	97.1
Prescribe IA in patients with CBI caused by *P. aeruginosa* or other non-fermenting gram-negative bacilli (Table 1), given their special virulence	2.9	↓	97.1
Treat patients with CBI caused by other PPMs, with clinical and functional deterioration or frequent infectious exacerbations, with long-term macrolides. If positive cultures and poor disease control persist, start IA	2.9	2.9	94.2
The decision to administer a specific AI or another depends not on the susceptibility testing, but on the PPM. An IA to which the PPM family is known to be susceptible must be selected	2.9	↓	97.1
The dosage is the same as that used in bronchiectasis (Table 5)	↓	↓	100
Maintain treatment as long as a clinical benefit is observed, i.e., the least purulent sputum possible according to the sputum color scale in Fig. 2 and reduction of exacerbations. Assess withdrawal after 6 months in case of clinical stability and negative cultures. In this case, close microbiological monitoring will continue, and if CBI reappears, give long-term treatment	↓	2.9	97.1
Given the possible risk of allergy, bronchospasm, dyspnea, cough, or hemoptysis, take certain precautions when administering IA: education on the use and maintenance of devices; preinhalation of fast-acting bronchodilators; administer the first dose in the hospital setting; in severe COPD (FEV_1 < 50%), consider the risk of IA-induced bronchoconstriction, assessing the possibility of performing spirometry before and after the first dose (decline in $FEV_1 \geq 15\%$)	↓	5.8	94.2
Assess the risk of nephrotoxicity and ototoxicity caused by aminoglycosides: avoid their use in severe chronic renal insufficiency; perform 6-monthly clinical laboratory testing during the first year (then annually); evaluate hearing loss during treatment	↓	↓	100
If the patient performs bronchial drainage techniques or receives nebulized hypertonic saline therapy, these treatments should precede IA	↓	↓	100

Table 7 (*Continued*)

	Disagree (score 1 or 2)	Indifferent (score 3)	Agree (score 4 or 5)
Module 6. Long-term macrolide treatment			
Start macrolide treatment in stable patients with 3 or more exacerbations/year (moderate or severe, requiring antibiotic treatment), despite the correct core treatment	2.9	5.8	91.3
In the case of CBI due to *P. aeruginosa*, monotherapy with macrolides is inadvisable; instead, these compounds should be combined with IA	5.8	8.5	85.7
The regimens supported by the most evidence are: azithromycin 500 mg/day, 3 days/week, or azithromycin 250 mg daily, for 1 year. Treatment will subsequently be individualized according to clinical response (reduction of exacerbations and expectoration) and the appearance of side effects	↓	↓	100
Due to the seasonal distribution of exacerbations, a treatment holiday may be considered during the warm months, if there has been a long period of stability without exacerbations and little mucous secretion. Consider restarting in autumn (or before, if exacerbations reappear).	2.9	11.4	85.7
Electrocardiogram, liver function tests, mycobacterial culture, and hearing evaluation should be performed before starting treatment. Assess whether to repeat these tests at least annually in prolonged treatments	↓	↓	100
Module 7. Inhaled corticosteroid therapy			
Special precautions must be taken with the use of ICS in patients with CBI	↓	5.8	94.2
If they are prescribed, consider using the lowest possible dose	2.9	↓	97.1
Re-evaluate the risk/benefit ratio of ICS use in patients who do not present: eosinophilia (persistently < 100 eosinophils/mm^3) or features consistent with concomitant asthma	5.8	2.9	91.3
Module 8. Other maintenance treatments			
A respiratory rehabilitation program (including health education, respiratory physiotherapy, muscle training, and physical activity programs) should be prescribed for patients with persistent expectoration, dyspnea grade ≥ 2, or low physical activity levels	↓	2.9	97.1
Prolonged treatment with N-acetyl cysteine or carbocysteine may be considered in COPD patients with frequent exacerbations	↓	11.4	88.6
A nutritional assessment should be made in patients with COPD and CBI, including at least: body mass index, **calorie intake**, and a longitudinal evaluation of progressive weight loss	↓	↓	100
Assess, according to the physician's criteria, the possible benefit of the use of probiotics in patients who require several antibiotic cycles per year, coinciding with each cycle, in order to avoid diarrhea and intestinal dysbiosis	↓	25.7	74.3
Module 9. Management of exacerbations in patients with COPD and chronic bronchial infection			
A sputum sample for culture should always be collected at the beginning of the exacerbation before starting antibiotic treatment	↓	2.9	97.1
A previous CBI should guide the choice of antibiotic according to the results of the last susceptibility testing (anticipated treatment) and the antibiotic susceptibility data of the hospital (Table 4)	↓	↓	100
Adjust treatment if the result of the new culture is different from the previous one or if the clinical course of the exacerbation is unfavorable	↓	↓	100
If during an exacerbation a different PPM is isolated from that which is causing the CBI, administer antibiotic treatment covering both PPMs (Table 4)	2.9	↓	97.1
In general, any exacerbation of COPD should assess risk factors for *P. aeruginosa* being involved	↓	↓	100
After an exacerbation involving a PPM, a follow-up culture should be performed at least 15 days after the end of antibiotic treatment whenever possible	2.9	8.5	88.6
Module 10. Follow-up of patients with COPD and chronic bronchial infection			
The initial follow-up after primary infection is determined by the need for microbiological monitoring (to assess eradication, reduction of bacterial load, or new PPMs) and clinical monitoring (reduction of symptoms and exacerbations)	↓	↓	100
Schedule follow-up visits scheduled depending on COPD severity, the frequency of exacerbations, and functional progress. In severe patients (GOLD D, FEV_1 < 50% and/or chronic respiratory failure), monitoring may be required at least every 3 months; in milder or more stable patients, visits may be performed every 4–6 months	↓	↓	100
During the first 2 years after the primary infection, consider monitoring the patient's microbiological status at each visit; schedule visits at longer intervals if the patient remains stable	5.8	11.4	82.8
At least 3 sputum samples/year should be obtained, and whenever an exacerbation associated with an increase in the amount or purulence of the sputum occurs, before starting antibiotic treatment	5.8	14.2	80
Perform at least 1 spirometry a year to detect patients with rapid decline. In patients who start IA, perform a spirometry every 3–6 months during the first year, and also after severe exacerbation or a change in maintenance	5.8	8.5	85.7

IA: inhaled antibiotic; ICS: Inhaled corticosteroids; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; CBI: chronic bronchial infection; PPM: potentially pathogenic microorganisms.

- During the first 2 years after the primary infection, consider monitoring the patient's microbiological status at each visit; schedule visits at longer intervals if the patient remains stable.
- At least 3 sputum samples/year should be obtained, and whenever an exacerbation associated with an increase in the amount or purulence of the sputum occurs, before starting antibiotic treatment.
- Perform at least 1 spirometry a year to detect patients with rapid decline.[24] In patients who start IA, perform a spirometry every 3–6 months during the first year, and also after severe exacerbation or a change in maintenance treatment.

Conclusions

This document aims to provide clinicians with guidelines on how to detect, define, and treat COPD patients in whom PPMs are frequently or infrequently isolated. Given the shortage of publications on the subject, we decided to prepare a set of clinical recommendations on which consensus was reached among a broad group of experts, based on the scant literature and their abundant accumulated experience. Table 7 summarizes the statements contained in all 10 modules, all of which have achieved a broad degree of consensus. This set of recommendations will be continuously reviewed and its content will be updated as new scientific evidence emerges.

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Authors' contribution to the study

Conception and design: DDRC, JLLC, MAMG.

Data acquisition: all authors.

Draft manuscript and critical review of intellectual content: all authors.

Final approval of the version submitted: all authors.

Conflict of interests

The authors declare that they have no conflict of interests directly or indirectly related with the contents of this manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arbr.2020.08.006.

References

1. Matkovic Z, Miravitlles M. Chronic bronchial infection in COPD. Is there an infective phenotype? Respir Med. 2013;107(1):10–22.
2. Zakharkina T, Heinzel E, Koczulla RA, Greulich T, Rentz K, Pauling JK, et al. Analysis of the airway microbiota of healthy individuals and patients with chronic obstructive pulmonary disease by T-RFLP and clone sequencing. PLoS One. 2013;8(7):e68302.
3. Kolsum U, Donaldson GC, Singh R, Barker BL, Gupta V, George L, et al. Blood and sputum eosinophils in COPD; relationship with bacterial load. Respir Res. 2017;18(1):88.
4. Marin A, Garcia-Aymerich J, Sauleda J, Belda J, Millares L, García-Núñez M, PAC-COPD Study Group, et al. Effect of bronchial colonisation on airway and systemic inflammation in stable COPD. COPD. 2012;9:121–30.
5. Soler N, Torres A, Ewig S, Gonzalez J, Celis R, et al. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J RespirCrit Care Med. 1998;157 5 Pt 1:1498–505.
6. Leung JM, Tiew PY, Mac Aogáin M, Budden KF, Yong VF, Thomas SS, et al. The role of acute and chronic respiratory colonization and infections in the pathogenesis of COPD. Respirology. 2017;22(4):634–50.
7. Sethi S, Maloney J, Grove L, Wrona C, Berenson CS. Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;173(9):991–8.
8. Marin A, Monsó E, Garcia-Nuñez M, Sauleda J, Noguera A, Pons J, et al. Variability and effects of bronchial colonisation in patients with moderate COPD. EurRespir J. 2010;35(2):295–302.
9. Barker BL, Haldar K, Patel H, Pavord ID, Barer MR, Brightling CE, et al. Association between pathogens detected using quantitative polymerase chain reaction with airway inflammation in COPD at stable state and exacerbations. Chest. 2015;147:46–55.
10. Singh R, Mackay AJ, Patel AR, Garcha DS, Kowlessar BS, Brill SE, et al. Inflammatory thresholds and the species-specific effects of colonising bacteria in stable chronic obstructive pulmonary disease. Respir Res. 2014;15:114.
11. Tufvesson E, Bjermer L, Ekberg M. Patients with chronic obstructive pulmonary disease and chronically colonized with Haemophilus influenzae during stable disease phase have increased airway inflammation. Int J Chron Obstruct Pulmon Dis. 2015;10:881–9.
12. Desai H, Eschberger K, Wrona C, Grove L, Agrawal A, Grant B, et al. Bacterial colonization increases daily symptoms in patients with chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2014;11(3):303–9.
13. Wilkinson TM, Patel IS, Wilks M, Donaldson GC, Wedzicha JA. Airway bacterial load and FEV1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;167(8):1090–5.
14. Bafadhel M, Haldar K, Barker B, Patel H, Mistry V, Barer MR, et al. Airway bacteria measured by quantitative polymerase chain reaction and culture in patients with stable COPD: relationship with neutrophilic airway inflammation, exacerbation frequency, and lung function. Int J Chron Obstruct Pulmon Dis. 2015;10:1075–83.
15. Zhang M, Li Q, Zhang XY, Ding X, Zhu D, Zhou X. Relevance of lower airway bacterial colonization, airway inflammation, and pulmonary function in the stable stage of chronic obstructive pulmonary disease. Eur J ClinMicrobiol Infect Dis. 2010;29:1487–93.
16. Banerjee D, Khair OA, Honeybourne D. Impact of sputum bacteria on airway inflammation and health status in clinical stable COPD. EurRespir J. 2004;23(5):685–91.
17. Braeken DC, Houben-Wilke S, Smid DE, Rohde GG, Drijkoningen JJ, Wouters EF, et al. Sputum microbiology predicts health status in COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2741–8.

18. Patel IS, Seemungal TA, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. Thorax. 2002;57(9):759–64.
19. Choi J, Oh JY, Lee YS, Hur GY, Lee YS, Shim JJ, et al. Pseudomonas aeruginosa infection increases the readmission rate of COPD patients. Int J Chron Obstruct Pulmon Dis. 2018;13:3077–83.
20. Almagro P, Salvadó M, Garcia-Vidal C, Rodríguez-Carballeira M, Cuchi E, Torres J, et al. *Pseudomonas aeruginosa* and mortality after hospital admission for chronic obstructive pulmonary disease. Respiration. 2012;84(1):36–43.
21. Jacobs DM, Ochs-Balcom HM, Noyes K, Zhao J, Leung WY, Pu CY, et al. Impact of *Pseudomonas aeruginosa* Isolation on Mortality and Outcomes in an Outpatient Chronic Obstructive Pulmonary Disease Cohort. Open Forum Infect Dis. 2020;7(1):ofz546.
22. Mammen MJ, Sethi S. COPD and the microbiome. Respirology. 2016;21(4):590–9.
23. Miravitlles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish Guidelines for Management of Chronic Obstructive Pulmonary Disease (GesEPOC) 2017. Pharmacological treatment of stable phase. Arch Bronconeumol. 2017;53:324–35.
24. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J. 2019;53.
25. Sapru K, Hill AT. Advances in bronchiectasis. Clinical medicine (London, England). 2019;19(3):230–3.
26. Einarsson GG, Comer DM, McIlreavey L, Parkhill J, Ennis M, Tunney MM, et al. Community dynamics and the lower airway microbiota in stable chronic obstructive pulmonary disease, smokers and healthy non-smokers. Thorax. 2016;71(9):795–803.
27. Erb-Downward JR, Thompson DL, Han MK, Freeman CM, McCloskey L, Schmidt LA, et al. Analysis of the lung microbiome in the ‘healthy’ smoker and in COPD. PloS one. 2011;6(2):e16384.
28. Cox MJ, Turek EM, Hennessy C, Mirza GK, James PL, Coleman M, et al. Longitudinal assessment of sputum microbiome by sequencing of the 16S rRNA gene in non-cystic fibrosis bronchiectasis patients. PloS one. 2017;12(2):e0170622.
29. Caverly LJ, Huang YJ, Sze MA. Past, Present, and Future Research on the Lung Microbiome in Inflammatory Airway Disease. Chest. 2019;156(2):376–82.
30. Miravitlles M, Espinosa C, Fernández-Laso E, Martos JA, Maldonado JA, Gallego M. 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):40–6.
31. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, et al. Canadian Thoracic Society. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can Respir J. 2007;14 Suppl B:5B–32B.
32. Lode H, Allewelt M, Balk S, De Roux A, Mauch H, Niederman M, et al. A prediction model for bacterial etiology in acute exacerbations of COPD. Infection. 2007;35(3):143–9.
33. Santos S, Marin A, Serra-Batlles J, de la Rosa D, Solanes I, Pomares X, et al. Treatment of patients with COPD and recurrent exacerbations: the role of infection and inflammation. Int J Chron Obstruct Pulmon Dis. 2016;11:515–25.
34. Hill AT, Campbell EJ, Hill SL, Bayley DL, Stockley RA. Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. Am J Med. 2000;109(4):288–95.
35. Murphy TF. *Pseudomonas aeruginosa* in adults with chronic obstructive pulmonary disease. CurrOpinPulm Med. 2009;15(2):138–42.
36. Parameswaran GI, Sethi S. Pseudomonas infection in chronic obstructive pulmonary disease. Future Microbiol. 2012;7(10):1129–32.
37. Eklöf J, Sørensen R, Ingebrigtsen TS, Sivapalan P, Achir I, Boel JB, et al. *Pseudomonas aeruginosa* and risk of death and exacerbations in patients with chronic obstructive pulmonary disease: an observational cohort study of 22053 patients. Clin Microbiol Infect. 2020;26(2):227–34.
38. Máiz L, Nieto R, Cantón R, Gómez G, de la Pedrosa E, Martinez-García MÁ. Fungi in Bronchiectasis: A Concise Review. Int J Mol Sci. 2018;19(1).
39. Bafadhel M, McKenna S, Agbetile J, Fairs A, Desai D, Mistry V, et al. Aspergillus fumigatus during stable state and exacerbations of COPD. EurRespir J. 2014;43(1):64–71.
40. Donohue MJ. Increasing nontuberculous mycobacteria reporting rates and species diversity identified in clinical laboratory reports. BMC Infect Dis. 2018;18(1):163.
41. Huang CT, Tsai YJ, Wu HD, Wang JY, Yu CJ, Lee LN, et al. Impact of non-tuberculous mycobacteria on pulmonary function decline in chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2012;16(4):539–45.
42. Murray PR, Washington JA. Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin. Proc. 1975;50(6):339–44.
43. Koo HK, Park SW, Park JW, Choi HS, Kim TH, Yoon HK, et al. Chronic cough as a novel phenotype of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2018;13:1793–801.
44. Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a comorbidity of chronic obstructive pulmonary disease: a systematic review and meta-analysis. PloS One. 2016;11(3):e0150532.
45. Ni Y, Shi G, Yu Y, Hao J, Chen T, Song H. Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2015;10:1465–75.
46. Miravitlles M, Marín A, Monsó E, Vilà S, de la Roza C, Hervás R, et al. Colour of sputum is a marker for bacterial colonisation in chronic obstructive pulmonary disease. Respir Res. 2010;11:58.
47. Murray MP, Pentland JL, Turnbull K, MacQuarrie S, Hill AT. Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. EurRespir J. 2009;34(2):361–4.
48. Hsieh MH, Lin CY, Wang CY, Fang YF, Lo YL, Lin SM, et al. Impact of concomitant nontuberculous mycobacteria and *Pseudomonas aeruginosa* isolates in non-cystic fibrosis bronchiectasis. Infect Drug Resist. 2018;11:1137–43.
49. Chu H, Zhao L, Xiao H, Zhang Z, Zhang J, Gui T, et al. Prevalence of nontuberculous mycobacteria in patients with bronchiectasis: a meta-analysis. Arch Med Sci. 2014;10(4):661–8.
50. Hosono Y, Kitada S, Yano Y, Mori M, Miki K, Miki M, et al. The association between erythromycin monotherapy for Mycobacterium avium complex lung disease and cross-resistance to clarithromycin: A retrospective case-series study. J Infect Chemother. 2018;24(5):353–7.
51. Martínez-García MÁ, Máiz L, Olveira C, Girón RM, de la Rosa D, Blanco M, et al. Spanish Guidelines on the Evaluation and Diagnosis of Bronchiectasis in Adults. Arch Bronconeumol. 2018;54(2):79–87.
52. Martinez-Garcia MA, de la Rosa-Carrillo D, Soler-Cataluña JJ, Catalan-Serra P, Ballester M, Roca Vanaclocha Y, et al. Bronchial infection and temporal evolution of bronchiectasis in patients with chronic obstructive pulmonary disease. Clin Infect Dis. 2020. Jan 22. pii: ciaa069. doi: 10.1093/cid/ciaa069. [Epub ahead of print].
53. Hurst JR, Elborn JS, De Soyza A. COPD-bronchiectasis overlap syndrome. Eur Respir J. 2015;45:310–3.
54. Gatheral T, Kumar N, Sansom B, Lai D, Nair A, Vlahos I, et al. COPD-related bronchiectasis; independent impact on disease course and outcomes. COPD. 2014;11(6):605–14.
55. Martínez-García MA, de la Rosa Carrillo D, Soler-Cataluña JJ, Donat-Sanz Y, Serra PC, Lerma MA, et al. Prognostic value of bronchiectasis in patients with moderate-to-severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;187(8):823–31.
56. Martínez-García MA, Soler-Cataluña JJ, Donat Sanz Y, Catalán Serra P, Agramunt Lerma M, Ballestín Vicente J, et al. Factors associated with bronchiectasis in patients with COPD. Chest. 2011;140(5):1130–7.
57. Martinez-García MA, Miravitlles M. Bronchiectasis in COPD patients: more than a comorbidity? Int J Chron Obstruct Pulmon Dis. 2017;12:1401–11.
58. Crisafulli E, Guerrero M, Ielpo A, Ceccato A, Huerta A, Gabarrús A, et al. Impact of bronchiectasis on outcomes of hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease: A propensity matched analysis. Sci Rep. 2018;8:9236.
59. Chalmers JD, Aliberti S, Filonenko A, Shteinberg M, Goeminne PC, Hill AT, et al. Characterisation of the “frequent exacerbator phenotype” in bronchiectasis. Am J Respir Crit Care Med. 2018;197:1410–20.
60. Jairam PM, van der Graaf Y, Lammers JW, Mali WP, de Jong PA. PROVIDI Study group. Incidental findings on chest CT imaging are associated with increased COPD exacerbations and mortality. Thorax. 2015;70(8):725–31.
61. Zoumot Z, Wilson R. Respiratory infection in noncystic fibrosis bronchiectasis. Curr Opin Infect Dis. 2010;23:165–70.
62. Estirado C, Ceccato A, Guerrero M, Huerta A, Cilloniz C, Vilaró O, et al. Microorganisms resistant to conventional antimicrobials in acute exacerbations of chronic obstructive pulmonary disease. Respir Res. 2018;19:119.
63. Martínez-García MÁ, Máiz L, Olveira C, Girón RM, de la Rosa D, Blanco M, et al. Spanish Guidelines on Treatment of Bronchiectasis in Adults. Arch Bronconeumol. 2018;54(2):88–98.
64. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn JS, Floto RA, et al. British Thoracic Society guideline for bronchiectasis in adults. BMJ Open Respir Res. 2018;5(1):e000348.
65. Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. EurRespir J. 2017;50:1700629.
66. Murphy TF, Brauer AL, Eschberger K, Lobbins P, Grove L, Cai X, et al. *Pseudomonas aeruginosa* in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177(8):853–60.
67. Rodrigo-Troyano A, Melo V, Marcos PJ, Laserna E, Peiro M, Suarez-Cuartin G, et al. *Pseudomonas aeruginosa* in Chronic Obstructive Pulmonary Disease Patients with Frequent Hospitalized Exacerbations: A Prospective Multicentre Study. Respiration. 2018;96:417–24.
68. Cantón R, Maiz L, Escribano A, Olveira C, Oliver A, Asensio O, et al. Spanish consensus on the prevention and treatment of *Pseudomonas aeruginosa* bronchial infections in cystic fibrosis patients. Arch Bronconeumol. 2015;51:140–50.
69. Finney LJ, Ritchie A, Pollard E, Johnston SL, Mallia P. Lower airway colonization and inflammatory response in COPD: a focus on Haemophilus influenzae. Int J Chron Obstruct Pulmon Dis. 2014;9:1119–32.
70. Sriram KB, Cox AJ, Clancy RL, Slack MPE, Cripps AW. Nontypeable Haemophilus influenzae and chronic obstructive pulmonary disease: a review for clinicians. Crit Rev Microbiol. 2018;44(2):125–42.
71. Máiz L, Girón RM, Olveira C, Quintana E, Lamas A, Pastor D, et al. Inhaled antibiotics for the treatment of chronic bronchopulmonary *Pseudomonas aeruginosa* infection in cystic fibrosis: systematic review of randomized controlled trials. Expert Opin Pharmacother. 2013;14(9):1135–49.
72. Martinez-Garcia MA, Soler-Cataluña JJ, Catalan P. Antibióticos inhalados en el tratamiento de las bronquiectasias no debidas a fibrosis quística. Arch Bronconeumol. 2011;47 Suppl 3:8–13.

73. Dalhoff A. Pharmacokinetics and pharmacodynamics of aerosolized antibacterial agents in chronically infected cystic fibrosis. ClinMicrobiol Rev. 2014;27:753.
74. Rubin BK. Aerosolized antibiotics for non-cystic fibrosis bronchiectasis. J Aerosol Med Pulm Drug Deliv. 2008;21:71–6.
75. Dal Negro R, Micheletto C, Tognella S, Visconti M, Turati C. Tobramycin nebulizer solution in severe COPD patients colonized with *Pseudomonas aeruginosa*: effects on bronchial inflammation. Adv Ther. 2008;25:1019–30.
76. Berlana D, Llop JM, Manresa F, Jódar R. Outpatient treatment of *Pseudomonas aeruginosa* bronchial colonization with long-term inhaled colistin, tobramycin, or both in adults without cystic fibrosis. Pharmacotherapy. 2011;31(2):146–57.
77. Nijdam LC, Assink MD, Kuijvenhoven JC, de Saegher ME, van der Valk PD, van der Palen J, et al. Safety and Tolerability of Nebulized Amoxicillin-Clavulanic Acid in Patients with COPD (STONAC 1 and STONAC 2). COPD. 2016;13(4):448–54.
78. Bruguera N, Marin A, Garcia-Olive I, Radua J, Prat C, Gil M, et al. Effectiveness of treatment with nebulized colistin in patients with COPD. Int J Chron Pulmon Dis. 2017;12:2909–15.
79. Montón C, Prina E, Pomares X, Cugat JR, Casabella A, Oliva JC, et al. Nebulized Colistin And Continuous Cyclic Azithromycin In Severe COPD Patients With Chronic Bronchial Infection Due To *Pseudomonas aeruginosa*: A Retrospective Cohort Study. Int J Chron Obstruct Pulmon Dis. 2019;14:2365–73.
80. Sethi S, Jones PW, Theron MS, Miravitlles M, Rubinstein E, Wedzicha JA, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: A randomized control trial. Respiratory Research. 2010;11:10.
81. Drobnic ME, Sune P, Montoro JB, Ferrer A, Orriols R. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa*. Ann Pharmacother. 2005;39:39–44.
82. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. Chest. 2005;127:14206.
83. Navas B, Vaquero JM, Santos F, Cobos MJ, Fernández MC, Muñoz L. Impacto clínico y evolución microbiológica tras tratamiento con tobramicina inhalada en bronquiectasias colonizadas por *Pseudomonas aeruginosa*. Neumosur. 2008;20:129–33.
84. Dennis BB, Rinaldi G, Housley G, Shah A, Shah OA, Loebinger MR. The utility of drug reaction assessment trials for inhaled therapies in patients with chronic lung diseases. Respir Med. 2018;140:122–6.
85. Ficha técnica TOBI. Dsiponible en https://cima.aemps.es/cima/pdfs/es/ft/63689/63689_ft.pdf.
86. Simpson JL, Powell H, Baines KJ, Milne D, Coxson HO, Hansbro PM, et al. The effect of azithromycin in adults with stable neutrophilic COPD: a double blind randomised, placebo controlled trial. PLoS One. 2014;9(8):e105609.
87. Uzun S, Djamin RS, Kluytmans JA, Mulder PG, van't Veer NE, Ermens AA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2014;2(5):361–8.
88. Herath SC, Normansell R, Maisey S, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2018;10:CD009764.
89. Naderi N, Assayag D, Mostafavi-Pour-Manshadi SM, Kaddaha Z, Joubert A, Ouellet I, et al. Long-term azithromycin therapy to reduce acute exacerbations in patients with severe chronic obstructive pulmonary disease. Respir Med. 2018;138:129–36.
90. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011;365:689–98.
91. Wang Y, Zijp TR, Bahar MA, Kocks JWH, Wilffert B, Hak E. Effects of prophylactic antibiotics on patients with stable COPD: a systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2018;73:3231–43.
92. Wedzicha J, Calverley P, Albert R, Anzueto A, Criner G, Hurst J, et al. Prevention of COPD exacerbations: An European Respiratory Society/American Thoracic Society (ERS/ATS) guideline. Eur Respir J. 2017;50:1602265.
93. Sun S, Laden F, Hart JE, Qiu H, Wang Y, Wong CM, et al. Seasonal temperature variability and emergency hospital admissions for respiratory diseases: a population-based cohort study. Thorax. 2018;73:951–8.
94. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. The Cochrane database of systematic reviews. 2014;(3):Cd010844.
95. Singanayagam A, Glanville N, Girkin JL, Ching YM, Marcellini A, Porter JD, et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. Nature communications. 2018;9(1):2229.
96. Singanayagam A, Glanville N, Cuthbertson L, Bartlett NW, Finney LJ, Turek E, et al. Inhaled corticosteroid suppression of cathelicidin drives dysbiosis and bacterial infection in chronic obstructive pulmonary disease. Science translational medicine. 2019;11(507).
97. Contoli M, Pauletti A, Rossi MR, Spanevello A, Casolari P, Marcellini A, et al. Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. Eur Respir J. 2017;50(4).
98. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014;3:CD010115.
99. Martínez-García MA, Faner R, Oscullo G, la Rosa-Carrillo D, Soler-Cataluña JJ, Ballester M, et al. Inhaled Steroids, Circulating Eosinophils, Chronic Airway Infection and Pneumonia Risk in Chronic Obstructive Pulmonary Disease: A Network Analysis. Am J Respir Crit Care Med. 2020, doi: 10.1164/rccm.201908-1550OC. [Epub ahead of print].
100. Yang M, Chen H, Zhang Y, Du Y, Xu Y, Jiang P, et al. Long-term use of inhaled corticosteroids and risk of upper respiratory tract infection in chronic obstructive pulmonary disease: a meta-analysis. Inhal Toxicol. 2017;29(5):219–26.
101. Liu VX, Winthrop KL, Lu Y, Sharifi H, Nasiri HU, Ruoss SJ. Association between Inhaled Corticosteroid Use and Pulmonary Nontuberculous Mycobacterial Infection. Ann Am Thorac Soc. 2018;15(10):1169–76.
102. Brode SK, Campitelli MA, Kwong JC, Lu H, Marchand-Austin A, Gershon AS, et al. The risk of mycobacterial infections associated with inhaled corticosteroid use. Eur Respir J. 2017;50(3).
103. Richardson CR, Franklin B, Moy ML, Jackson EA. Advances in rehabilitation for chronic diseases: improving health outcomes and function. BMJ. 2019;365:l2191.
104. Martí JD, Muñoz G, Gimeno-Santos E, Balañá A, Vilaró J. Análisis descriptivo de la fisioterapia respiratoria en España. Rehabilitación (Madr). 2016;50(3):160–5.
105. Blondeel A, Demeyer H, Janssens W, Troosters T. The role of physical activity in the context of pulmonary rehabilitation. COPD. 2018;15(6):632–9.
106. Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2019;5:Cd001287.
107. Tse HN, Raiteri L, Wong KY, Yee KS, Ng LY, Wai KY, et al. High-dose Nacetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. Chest. 2013;144:106–18.
108. Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, et al. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. Lancet Respir med. 2014;2:187–94.
109. Paone G, Lanata L, Saibene F, Toti S, Palermo P, Graziani C, et al. A prospective study of the effects of carbocysteine lysine salt on frequency of exacerbations in COPD patients treated with or without inhaled steroids. Eur Rev Med Pharmacol Sci. 2019;23(15):6727–35.
110. Scoditti E, Massaro M, Garbarino S, Toraldo DM. Role of Diet in Chronic Obstructive Pulmonary Disease Prevention and Treatment. Nutrients. 2019;11(6).
111. Tabak C, Smit HA, Heederik D, Ocke MC, Kromhout D. Diet and chronic obstructive pulmonary disease: independent beneficial effects of fruits, whole grains, and alcohol (the MORGEN study). Clinical and experimental allergy. 2001;31(5):747–55.
112. Romieu I, Trenga C. Diet and obstructive lung diseases. Epidemiologic reviews. 2001;23(2):268–87.
113. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database Syst Rev. 2015;(2):CD006895.
114. Alexandre Y, Le Blay G, Boisramé-Gastrin S, Le Gall F, Héry-Arnaud G, Gouriou S, et al. Probiotics: a new way to fight bacterial pulmonary infections? Med Mal Infect. 2014;44(1):9–17.
115. Pattani R, Palda VA, Hwang SW, Shah PS. Probiotics for the prevention of antibiotic-associated diarrhea and Clostridium difficile infection among hospitalized patients: systematic review and meta-analysis. Open Med. 2013;7(2):e56–67.
116. Goldenberg JZ, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev. 2017;12:CD006095.
117. Dietrich CG, Kottmann T, Alavi M. Commercially available probiotic drinks containing Lactobacillus casei DN-114001 reduce antibiotic-associated diarrhea. World J Gastroenterol. 2014;20(42):15837–44.
118. Sethi S, Murphy TF. Infection in the Pathogenesis and Course of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2008;359:2355–65.
119. Sethi S, Evans N, Grant BJB, Murphy TF. New Strains of Bacteria and Exacerbations of Chronic Obstructive Pulmonary Disease. N Engl J Med. 2002;347:465–71.
120. Monsó E. Microbiome in chronic obstructive pulmonary disease. Ann Transl Med. 2017;5(12):251.
121. Huang YJ, Sethi S, Murphy T, Nariya S, Boushey HA, Lynch SV. Airway microbiome dynamics in exacerbations of chronic obstructive pulmonary disease. Clin. Microbiol. 2014;52(8):2813–23.
122. Garcia-Nuñez M, Marti S, Puig C, Perez-Brocal V, Millares L, Santos S, et al. Bronchial microbiome, PA biofilm-forming capacity and exacerbation in severe COPD patients colonized by *P. aeruginosa*. Future Microbiol. 2017;12:379–92.
123. Rosell A, Monsó E, Soler N, Torres F, Angrill J, Riise G, et al. Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. Arch Intern Med. 2005;165(8):891–7.
124. Simpson JL. COPD is characterized by increased detection of Haemophilus influenzae, Streptococcus pneumoniae and a deficiency of Bacillus species. Respirology. 2016;21(4):697–704.
125. Ghosh B, Gaike AH, Pyasi K, Brashier B, Das VV, Londhe JD, et al. Bacterial load and defective monocyte-derived macrophage bacterial phagocytosis in biomass smoke-related COPD. Eur Respir J. 2019;53(2).
126. Garcha DS. Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. Thorax. 2012;67(12):1075–80.
127. Tumkaya, et al. Relationship between airway colonization, inflammation and exacerbation frequency in COPD. Respir Med. 2007;101(4):729–37.

128. Seo Kw, Hwang Sj, Sung Sj, Kim Sj, Do Gw, Hur Sj, et al. Bacteriologic Analysis of Expectorated Sputum in Patient with Bronchiectasis. Tuberc Respir Dis. 2009;67(6):517–27.
129. Rangelov K, Sethi S. Role of infections. Clin Chest Med. 2014;35(1):87–100.
130. Wang H, Gu X, Weng Y, Xu T, Fu Z, Peng W, et al. Quantitative analysis of pathogens in the lower respiratory tract of patients with chronic obstructive pulmonary disease. BMC Pulm Med. 2015;15:94.
131. Everaerts S, Lagrou K, Dubbeldam A, Lorent N, Vermeersch K, Van Hoeyveld E, et al. Sensitization to Aspergillus fumigatus as a risk factor for bronchiectasis in COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:2629–38.
132. Miravitlles M, Sliwinski P, Rhee CK, Costello RW, Carter V, Tan J, et al. Evaluation of criteria for clinical control in a prospective, international, multicenter study of patients with COPD. Respir Med. 2018;136:8–14.
133. Soler-Cataluña JJ, Marzo M, Catalán P, Miralles C, Alcazar B, Miravitlles M. Validation of clinical control in COPD as a new tool for optimizing treatment. Int J Chron Obstruct Pulmon Dis. 2018;13:3719–31.
134. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648–54.
135. Soler-Cataluña JJ, Martínez-García MA, Sánchez LS, Tordera MP, Sánchez PR. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. Respir Med. 2009;103(5):692–9.
136. Miravitlles M, Dirksen A, Ferrarotti I, Koblizek V, Lange P, Mahadeva R, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha1-antitrypsin deficiency. Eur Respir J. 2017;50.