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Decalogue for the selection of oral antibiotics for lower respiratory tract infections

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ABSTRACT

Lower respiratory tract infections, including chronic obstructive pulmonary disease exacerbations (COPD-E) and community acquired pneumonia (CAP), are one of the most frequent reasons for consultation in primary care and hospital emergency departments, and are the cause of a high prescription of antimicrobial agents. The selection of the most appropriate oral antibiotic treatment is based on different aspects and includes to first consider a bacterial aetiology and not a viral infection, to know the bacterial pathogen that most frequently cause these infections and the frequency of their local antimicrobial resistance. Treatment should also be prescribed quickly and antibiotics should be selected among those with a quicker mode of action, achieving the greatest effect in the shortest time and with the fewest adverse effects (toxicity, interactions, resistance and/or ecological impact). Whenever possible, antimicrobials should be rotated and diversified and switched to the oral route as soon as possible. With these premises, the oral treatment guidelines for mild or moderate COPD-E and CAP in Spain include as first options beta-lactam antibiotics (amoxicillin and amoxicillin-clavulanate and cefditoren), in certain situations associated with a macrolide, and relegating fluoroquinolones as an alternative, except in cases where the presence of *Pseudomonas aeruginosa* is suspected.

Keywords: respiratory tract infections; bacterial infections; oral treatment; antibiotic use; antimicrobial resistance

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Decálogo para la selección del antibiótico oral en las infecciones respiratorias de vías bajas

RESUMEN

Las infecciones del tracto respiratorio inferior, incluyendo las exacerbaciones de la enfermedad pulmonar obstructiva crónica (EPOC) y la neumonía adquirida en la comunidad (NAC), son uno de los motivos de consulta más frecuentes en atención primaria y los servicios de urgencias hospitalarios, y son la causa de una elevada prescripción de antimicrobianos. La selección del tratamiento oral más adecuado con antibióticos se basa en diferentes aspectos e incluye considerar en primer lugar una etiología bacteriana y no una infección vírica, conocer los patógenos bacterianos que más frecuentemente causa estas infecciones y la frecuencia local de su resistencia antimicrobiana. Además, el tratamiento debe prescribirse rápidamente y los antibióticos deben seleccionarse entre los que tienen un modo de acción más rápido, logrando el mayor efecto en el menor tiempo y con el menor número de efectos adversos (toxicidad, interacciones, resistencia y/o impacto ecológico). Siempre que sea posible, hay que rotar y diversificar los antimicrobianos y pasar a la vía oral lo antes posible. Con estas premisas, las guías de tratamiento oral de la exacerbación leve o moderada de la EPOC y NAC en España incluyen como primera opción los antibióticos betalactámicos (amoxicilina y amoxicilina-clavulánico y cefditoreno), en determinadas situaciones asociados a un macrólido, y relegando las fluoroquinolonas como alternativa, salvo en los casos en que se sospeche la presencia de *Pseudomonas aeruginosa*.

Palabras clave: infecciones del tracto respiratorio; infecciones bacterianas; tratamiento oral; uso de antimicrobianos; resistencia antimicrobiana,

INTRODUCTION

Lower respiratory tract infections (LRTI) are one of the most frequent reasons for consultation in primary care and hospital emergency departments, and are the cause of a high prescription of antimicrobial agents [1-3]. It is therefore necessary to consider a series of premises that guide their choice, especially in cases in which the patient's situation allows oral treatment, since their follow-up will be performed on an outpatient basis. For this reason, a group of professionals from the fields of primary care, hospital emergency medicine, internal medicine, infectious diseases, pneumology and clinical microbiology have proposed a Decalogue that summarises the criteria that, as a priority, should be taken into account when choosing oral antimicrobial treatment in exacerbations of chronic obstructive pulmonary disease (COPD) and community-acquired pneumonia (CAP). Many of the aspects listed here have been previously reviewed in greater depth [4-8]. This Decalogue is based on published scientific evidence and the personal experience of the panel of the authors. The recommendations are aligned with the principles of the National Plan against Antimicrobial Resistance (PRAN) of the Spanish Agency of Medicines and Health Products (AEMPS), which aims, among other objectives, to improve the prescription of this group of drugs in order to reduce antimicrobial resistance (https://www.resistenciaantibioticos.es/es, accessed 30 December 2021).

1.- IS THIS A BACTERIAL INFECTION?

The most common cause of COPD exacerbation is bacterial infection of the tracheobronchial tree. However, there are other possible aetiologies such as virus, contamination, thromboembolism or heart failure and the cause is not known in a third of cases. Identifying the aetiology that causes this exacerbation is of great importance in order to establish appropriate treatment. It is also important to identify patients who can be safely treated without antibiotics and to optimise treatment for those who need it [9]. In CAP, the majority is of bacterial aetiology, although in almost two thirds of patients it may remain unidentified, either because of a lack of microbiological diagnosis or because insufficient methods are used to identify the pathogen [10].

To identify a bacterial aetiology as the cause of the exacerbation, markers such as C-reactive protein and procalcitonin have been described, but the systematic usefulness of their use in these cases has not been established and their use in real life is very restricted [9]. A meta-analysis suggests that procalcitonin may be useful in reducing antibiotic prescribing, without affecting the rate of treatment failure, length of hospitalisation, recurrence or mortality [11]. However, due to the methodological limitations, the evidence is still low to moderate, so a general recommendation for the use of this or any other biomarker to establish the bacterial aetiology of an exacerbation cannot be established. A similar situation occurs in patients with CAP, where procalcitonin may be more useful in those cases where serial determinations are performed and as a guide in reducing the duration of antimicrobial therapy [12,13].

The classic Anthonisen criteria [14] for COPD exacerbation, based on clinical data of changes in symptomatology, increased dyspnoea, cough and sputum, and especially change in sputum colour, with all possible concerns, are still present in daily practice. The administration of antibiotics in COPD is more effective than placebo in exacerbations that meet at least two of the following three criteria: increased dyspnoea, sputum purulence or increased sputum volume. However, of

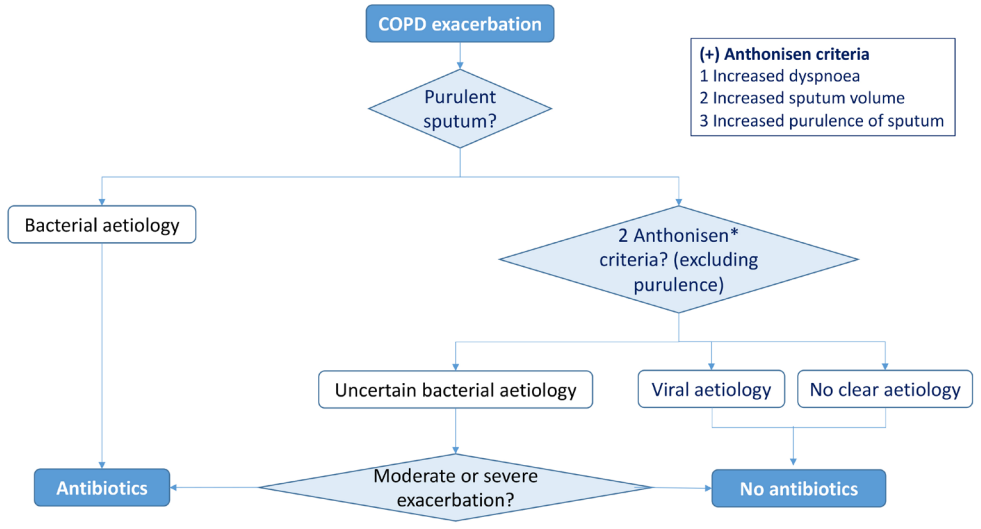

Figure 1 Suspicion of bacterial infection in COPD exacerbation and decision of antimicrobial treatment [modified from reference 9]

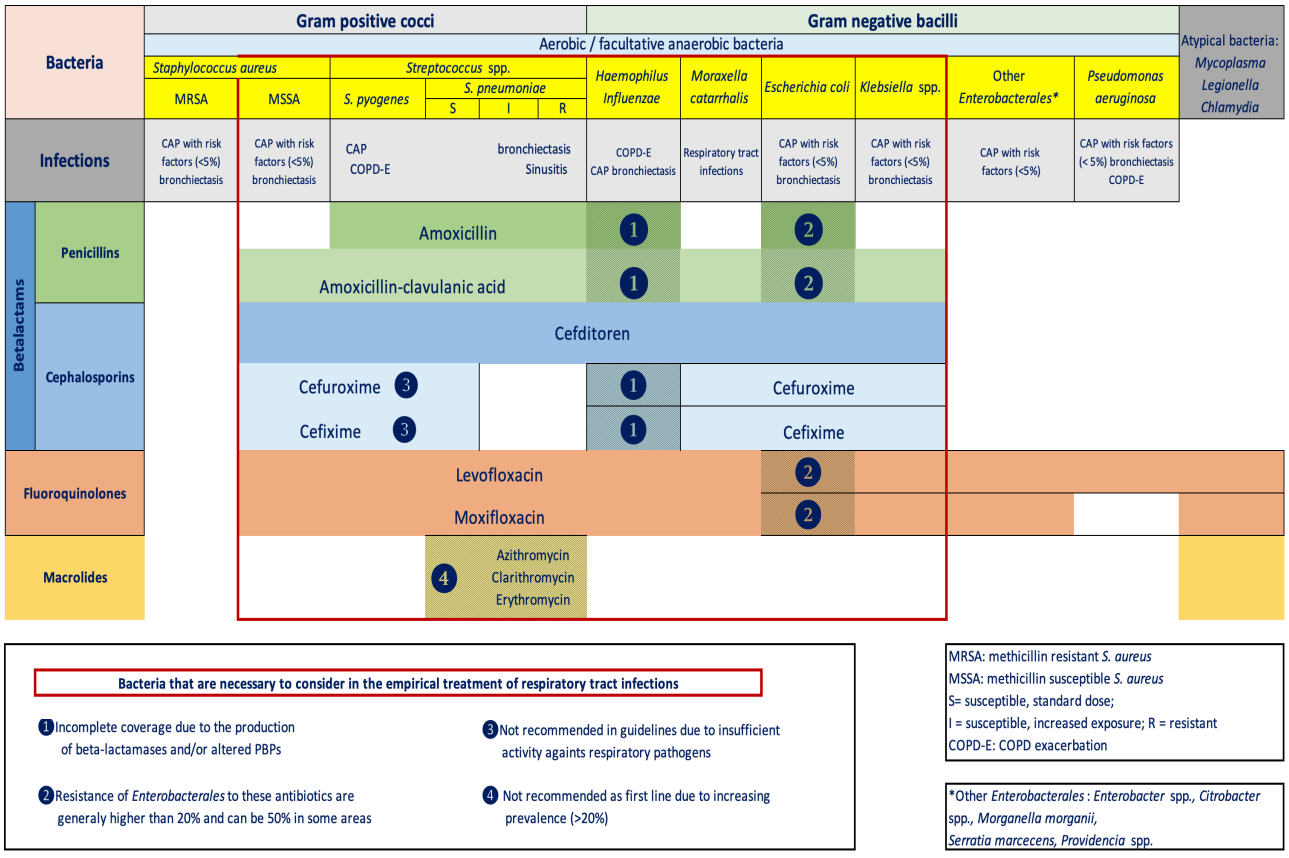

Figure 2 | **Antimicrobial spectrum of the main oral antibiotics in the treatment of lower respiratory tract infections [modified from reference 4].**

the three recommended criteria, the one that best predicts bacterial infection is the change in sputum colour and purulence [14,15] (Figure 1). In contrast, mucous sputum is rarely associated with bacterial infection [17] and in these cases other causes must be considered. Antibiotics are particularly indicated in severe COPD exacerbations and in the presence of purulent sputum. Sputum analysis (Gram stain and culture) is only indicated in patients with severe or very severe exacerbations, in those with frequent exacerbations, bronchiectasis, need for ventilation or in case of antibiotic treatment failure.

In CAP the diagnostic criteria are based on radiological changes and respiratory symptoms such as cough, purulent sputum, dyspnoea and chest pain, as well as fever. In patients with criteria for hospitalisation, Gram stain and culture are recommended as a minimum when sputum is purulent and detection of *Streptococcus pneumoniae* and *Legionella pneumophila* antigen [18].

2.- MOST LIKELY AETIOLOGY: MAXIMISING ERADICATION AND ADJUSTING SPECTRUM

Microbiological diagnosis in COPD exacerbations and CAP is difficult to establish, even when complex and invasive diagnostic methods are used. Although the possible role of the usual microbiota in LRTIs, especially in COPD exacerbation, is currently being discussed, the focus is on the microorganisms traditionally associated with these infections. In CAP, the aetiology is usually monomicrobial. Globally, the most frequent agent is *S. pneumoniae* (20-65%) [19] and should always be taken into account when establishing antibiotic coverage. With increasing age, the frequency of microorganisms classically referred to as "atypical" (*L. pneumophila, Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) decreases and the incidence of *Haemophilus influenzae* and Gram-negative bacilli increases [10,20,21]. In a smaller percentage of the cases, it may be due to viral agents (12-18%) and there may be associations of several pathogens (8-14%) [19]. However, the aetiology of CAP is conditioned by comorbidity, baseline functional status, severity of the acute episode, previously received antimicrobial treatments, contact with the hospital system or place of residence. Therefore, an aetiological approach according to risk factors for resistant microorganisms and severity level is also recommended [22].

In COPD exacerbations, the microorganisms involved vary

Table 1 **Susceptibility phenotypes and resistance mechanisms in *S. pneumoniae* and *H. influenzae* and the inferred prevalence in Spain [36-43].**

Phenotype	Penicillin	Ampicillin/ amoxicillin	Amoxicilin-clavulanate	Cefuroxime	Cefixime	Cefotaxime	Cefditoren	Imipenem / meropenem	Beta-lac-tamase	Altered PBPs	Prevalence
Streptococcus pneumoniae											
Pen-S, CTX-S (Wild type)	S	S	S	S	S	S	S	S	-	-	80-90%
Pen-I/R, CTX-S	I/R	I	I	I/R	I/R	S	S	S	-	1A,2X,SB	5-10%
Pen-S, CTX-I/R	S	I	I	R	R	I/R	I/R	S	-	2x	<1%
Pen-I, CTX-I/R	I	I	I	I/R	R	I/R	I/R	S	-	1A,2X	<1%
Pen-R, CTX-I/R	R	R	R	R	R	I/R	I/R	I/R	-	1A,2X,SB	2-5%
Haemophillus influenzae											
Wild Type	R	S	S	S	S	S	S	S	-		60-70%
BLPAR: β-lactamase-(+) ampicillin-resistant	R	R↑	S	S	S	S	S	S	TEM-1, ROB	-	20-30% (decreasing)
BLNAR: β-lactamase-(-) ampicillin-resistant	R	R↓	R↓	R	S↓	S	S	S	-	3	5-10% (increasing)
BLPACR: β-lactamase-(+) amoxicillin-clavulanate-resistant	R	R↑	R	R↓	S↓	S	S	S	TEM-1, ROB	3	<3% (increasing)

Arrows indicate low (R↓) and high level (R↑) resistance or decrease susceptibility (S↓).

according to the type of patient, risk factors and comorbidities. In many cases, they have been named "potentially pathogenic microorganisms" (PPMs) as they can be isolated both in the stable phase and during exacerbations [23,24]. *H. influenzae* is more prominent than in CAP, although *S. pneumoniae* and *M. catarrhalis* may also be present, and to a lesser extent, the so-called "atypicals" [25]. In older patients, *Pseudomonas aeruginosa*, other Gram-negative bacilli or even *Staphylococcus aureus* may also be isolated in microbiological cultures, especially in those with bronchiectasis [26]. Anaerobic microorganisms may be detected in COPD, especially in the stable phase. These tend to disappear or become less diverse during exacerbations and have therefore been assigned a protective value against PPM infection [27].

On the other hand, in the antibiotic treatment of CAP, we must try to achieve microbiological eradication, for which it is most convenient to use the most active antibiotics with the highest bactericidal activity against the possible causative pathogens and those that best meet the PK/PD parameters of clinical and microbiological efficacy. In COPD exacerbation, although the therapeutic objective should also be eradication, in practice reduction in the bacterial load is achieved, and a correlation can be established between this reduction and the appearance of a new exacerbation [28]. However, effectiveness, with the aim of achieving maximum microbiological eradication, must be achieved by using the antibiotic with the most restricted spectrum possible to the microorganisms most commonly isolated in this type of infection, in such a way as to minimise antibiotic selection pressure or alterations in the patient's microbiota. Currently, cefditoren, levofloxacin, moxifloxacin and amoxicillin-clavulanic acid in this order have the most appropriate spectrum over the most prevalent pathogens involved in COPD exacerbations and CAP. Moreover, they have also the most relevant PK/PD characteristics in these infections and are therefore included in most antimicrobial treatment guidelines [2,9,16,20,29-35] (Figure 2).

3.- KNOWING THE LOCAL RESISTANCE MAP

In addition to knowing the possible microorganisms involved in LRTI, it is always necessary to take into account the resistance mechanisms that may be present and to know their frequency at the local level. This will ensure better criteria in the choice of antimicrobial treatment. The latest report of the Instituto de Salud Carlos III, the reference center in Spain, which collects data on resistance of different pathogens, indicates that resistance rates to penicillin and third generation cephalosporins in *S. pneumoniae* have decreased over the years, reaching 21.7% and 6.0%, respectively, in 2020 [36]. Resistance to macrolides would be close to 25%, with simultaneous resistance to both compounds estimated at around 12%. These isolates are increasing in some serotypes not included in the thirteen-valent pneumococcal conjugate vaccine [37,38]. Surveillance studies conducted in Spain have shown that among oral cephalosporins, cefditoren has a similar behaviour to intravenous third-generation cephalosporins, with higher rates of resistance to cefaclor, cefuroxime and cefixime [39]. Resistance to fluoroquinolones is reported to be less than 2% [36].

Although there are few recent data in Spanish studies, resistance in *H. influenzae* due to production of beta-lactamases and conferring resistance to amoxicillin, but with sensitivity to amoxicillin-clavulanic acid, has stabilised at around 20-25%. On the other hand, and as in other countries, resistance to amoxicillin and oral cephalosporins such as cefaclor or cefuroxime, and sometimes to amoxicillin-clavulanic acid, is increasing [40,41]. Third-generation cephalosporins, cefotaxime or ceftriaxone, would not be affected, as would cefditoren, which maintains its activity in these isolates [38]. Beta-lactamase-producing strains with altered PBPs and combined resistance to amoxicillin, amoxicillin-clavulanic acid, oral cephalosporins and, to a lesser extent, third-generation cephalosporins, including cefditoren, are also increasing. As in *S. pneumoniae*, resistance to fluoroquinolones would be scarce and would be present mainly in patients with chronic bronchial infection and extensive exposure to this group of antimicrobials [41-43].

Recent data on *M. catarrhalis* are also scarce, although they indicate a high proportion of isolates with beta-lactamases (TEM or BRO) inhibited by clavulanic acid and low percentages of resistance to macrolides and fluoroquinolones [44,45].

M. pneumoniae is intrinsically resistant to penicillins, with macrolide resistance below 10%. In contrast, susceptibility to tetracyclines and fluoroquinolones is almost universal in this pathogen [46].

Finally, *P. aeruginosa* is intrinsically resistant to a large number of antimicrobials, narrowing oral therapeutic options to fluoroquinolones. Resistance figures may vary depending on the type of patient, being higher in those with chronic bronchial infection with previous treatment with this group of antimicrobials. In Spain, it would be higher than that found in other countries [47].

Table 1 shows the common susceptibility phenotypes in *S. pneumoniae* and *H. influenzae*, the associated resistance mechanism and the inferred prevalence of these phenotypes in Spain [36-43].

4.- TO BE QUICK IN ACTION AND EFFECT

In general, in most infectious syndromes and particularly in LRTI, the efficacy of antimicrobial treatment is fundament in two pillar: 1) control of the microbial inoculum (guided by the antimicrobial chosen) and 2) control of the focus (instrumental or surgical, organic or inorganic biofilm, ...). Derived from both actions, the speed of medical action in the execution of each control strategy and that of the antimicrobial activity translated into its bactericidal effect are essential elements. In fact, infection is an increasingly dynamic process and must be managed as a time-dependent code. In short, "time is money, and time is life".

To achieve these objectives in LRTIs, we must demand that the antimicrobial chosen has two important characteristics: 1) adequate antimicrobial spectrum and 2) optimal antimicrobial potency. Through its ability to cover the microbiological spectrum in an exacerbation of COPD or CAP, we will be sure to have antimicrobial activity against the main aetiological causes of these infectious syndromes, also taking into account the resistance characteristic of these microorganisms (point 3 of the Decalogue). Regarding the antimicrobial potency, we should select those antibiotics with a high activity translated into the ability to eliminate a greater number of microorganisms per unit of time, i.e. to achieve greater inhibition and, if possible, eradication of bacterial inoculum in the shortest possible time.

A bactericidal antibiotic is defined as an antibiotic with the ability to reduce ≥3 $\log_{10}$ (99.9%)/cfu/mL of the bacterial inoculum in a given period of time [48]. Examples of this group of antibiotics include beta-lactams, aminoglycosides and fluoroquinolones. Their bactericidal activity is generally determined by so-called lethality or kill curves, which measure the reduction of the bacterial inoculum over time. In general, a bacterial inoculum of 10^6 cfu/mL is assumed and the effect is measured over a period of less than 24 hours. An antibiotic is defined as bacteriostatic when the reduction in bacterial inoculum is <3 $\log_{10}$ cfu/mL over a given period of time. Examples of these other antibiotics include, among others, macrolides, clindamycin and tetracyclines. Furthermore, some antibiotics exhibit greater bactericidal activity at a higher dose or concentration of the drug at the site of infection and in a shorter period of time, i.e. the higher the dose of the antibiotic, the greater the bactericidal activity, and the faster as in the case of aminoglycosides. However, others maintain their bactericidal activity independently of the dose or concentration; this is the case of beta-lactams.

Therefore, in CAP and exacerbation of COPD and particularly in elderly patients or with comorbidities, antibiotics with faster action are more adequate [4,20]. This feature can improve the prognosis of the patients and avoid complications or sequels. When a comparison of the duration of the comorbidity period is made when compare treatments with antibiotics that achieve rapid decreases in bacterial concentration *versus* those that only produces slow decreases, the results are in favour of the formers. Antibiotics with high bactericidal capacity have a shorter comorbidity period and, therefore, an earlier and more stable period of normality, in contrast to antibiotics with low bactericidal capacity. This translates into better control of the patient's comorbidity, early clinical stabilisation, and a decrease in the average length of stay and its associated costs [49,50]. Late control of infection may even jeopardise patient survival as a result of decompensation of comorbidities.

The bactericidal activity of oral antibiotics used in the treatment of community-acquired LRTIs are clearly different against the main respiratory pathogens (*S. pneumoniae, H. influenzae* and *M. catarrhalis*) [5,51]. When comparing several of them (cefuroxime, cefpodoxime, cefixime, amoxicillin-clavulanic acid, cefditoren and levofloxacin), cefditoren and levofloxacin show a greater bactericidal effect in the $\log_{10}$ cfu/h reduction curves, both at 4 and 24 hours.

Another relevant aspect in the context of LRTIs is speed of reduction of inflammatory parameters, clinical recovery and

microbiological eradication [52]. In clinical studies of patients with COPD exacerbations comparing cefditoren *versus* levofloxacin, the clinical success rate in the overall study population was 78%, with a clinical cure rate of 80% in the cefditoren group and 75% in the levofloxacin group [53]. Overall, microbiological eradication in the test of cure was obtained in 85% of the total study population, although it was slightly higher for levofloxacin compared to cefditoren without statistically significant differences; a higher number of patients with moderate gastrointestinal adverse effects in the levofloxacin-treated group was observed. In addition, inflammatory parameters (such as interleukin-6) were significantly reduced in the test of cure with both cefditoren and levofloxacin compared to the first visit. Although no significant difference, the reduction was higher with cefditoren. The study concluded that this antibiotic represents a valid option in the treatment of mild to moderately severe cases of COPD exacerbation in the outpatient setting, as its use was associated with a significant rapid reduction in interleukin-6 and other biomarkers of lung inflammation and epithelial damage [53].

The relationship between antimicrobial activity and bactericidal activity is important for all the aspects mentioned above. Moreover, it is relevant for the prevention of selection of resistant strains at the focus of infection, in what would derive from the "fall and rise" theory in the case of COPD or in the avoidance of resistance emergence among the main community respiratory pathogens causing pneumonia through the concept called "selection window" and the "mutant prevention concentration" (MPC) indicator parameter (point 6 of this Decalogue).

5.- ANTIMICROBIAL TOLERANCE AND SAFETY

The oral antibiotics most commonly used in the treatment of LRTIs can generally be considered safe drugs [8]. Their adverse effects are infrequent and mild and rarely produce irreversible situations in the patients. Knowledge of clinically relevant adverse effects allows for a more judicious use of antibiotics based on the first principle of do no harm, *primun non nocere*, and the positioning of those that should be included in clinical treatment guidelines as first choice. However, in recent years, concerns have arisen with some of them, in particular fluoroquinolones, due to safety alerts generated by regulatory agencies, relegating them to a secondary position despite their excellent antimicrobial profile against respiratory pathogens associated with COPD exacerbation and CAP [54,55]. From a strict safety point of view, it is preferable to initiate treatment with a beta-lactam antibiotic as long as its efficacy is guaranteed according to the expected microorganism. Otherwise, a macrolide or, if appropriate, a fluoroquinolone may be chosen depending on the type and location of the infection and the patient [8]. On which antibiotic to choose within each class, the prioritisation seems clear in the case of beta-lactams, cefditoren over amoxicillin-clavulanic acid, and in the case of macrolides, azithromycin over the others, but it less so in the case of fluoroquinolones.

The adverse effects of antibiotics that affect their safety are due to different mechanisms including direct toxicity, interaction with other drugs, development of resistance and alteration of the microbiota [56]. The latter two are addressed in point 7 of this Decalogue. Toxicity is generally low at approved therapeutic doses and may be due to direct or indirect action on cells or tissues. These include mitochondrial dysfunction leading to organ damage and immunoparalysis. Damage can be caused by dose-dependent pharmacodynamics and pharmacokinetic interactions between the antibiotic and the eukaryotic cells and other drugs respectively, such as cardiac arrhythmias with fluoroquinolones and macrolides and collagen toxicity and neurotoxicity with fluoroquinolones. It is also caused by idiosyncratic immune-mediated reactions similar to anaphylaxis with effects ranging from rashes to toxic epidermal necrolysis or Stevens-Johnson syndrome [57].

Nausea, vomiting and diarrhoea are the most frequent adverse effects of oral antibiotics, but are particularly observed when clavulanic acid is administered at doses above 250 mg/day. As amoxicillin 500 mg and 875 mg tablets available in Spain contain more than 125 mg of clavulanic acid, the usual three-times-daily regimens increase the risk of vomiting and diarrhoea. In addition, amoxicillin-clavulanic acid is considered a hepatotoxic drug and has been associated with genetic variations in the HLA type II system, advanced age and the use of several courses of treatment [58,59]. Fluoroquinolones can produce different adverse effects, already discussed above. These are more frequent in patients with specific risk factors for each adverse effect [60] (Table 2).

In relation to interactions with other drugs, they usually occur by modification of their pharmacokinetic properties at different levels that affect absorption, protein binding, metabolism, especially by impact on cytochromes (CYP), elimination or other mechanisms such as serotonergic syndrome in the case of ciprofloxacin [57]. In these cases, there may be a change in the effect of the antibiotic or concomitant drug, which must be assessed in each patient and may require a change of regimen.

6.- MINIMISING TREATMENT DAYS

The length of an antibiotic treatment plays an important role in the development of antibiotic resistance [61,62]. Resistance induction and selection or resistant bacterial population increase with exposure time [61]. The traditional claim that early discontinuation of antibiotic treatment promotes antibiotic resistance is not supported by evidence [63,64]. On the contrary, longer duration of antibiotic treatment regimens has been associated with higher rates of resistance as it produces selective pressure not only on potential pathogens but also on microorganisms that are present in the usual microbiota [62,65].

There is evidence to support the safety and efficacy of short versus prolonged antibiotic treatment regimens for most common infections treated in outpatient care [66,67] and in more severe infections treated at the hospital level [68,69]. In

Table 2 Adverse effects due to fluoroquinolones related to patients at incremental risk [61].

Adverse effect	Patients at incremental risk
QT syndrome	Treatment with non-potassium-sparing diuretics or significant baseline bradycardia
Tendonitis	Older age, male, chronic renal disease, corticosteroid use
Retinal detachment	Age, past history, cataract surgery
Aortic dissection	Age, hypertension, congenital aortic valve anomalies, hereditary connective system disorders
Dysglycemias	Advanced age, diabetes, renal insufficiency and concurrent use of hypoglycemic drugs (especially sulphonylureas)
Psychiatric effects	Personal or family history

Table 3 General recommendations of length period of antimicrobial treatment in lower respiratory tract infections.

Infection	Administration	
	Route	Length in days
Mild	Oral	5
Moderate/severe	Oral	5 - 7
	Intravenous + oral	7 (2 intravenous + 5 oral)
Severe	Intravenous + oral	2-5 intravenous + 5 oral

addition, shortening antibiotic time has other advantages such as better adherence, fewer adverse effects and lower cost [65]. Treating bacterial infections for only as long as necessary is probably the safest and most feasible means of reducing unnecessary antibiotic use [70]. The duration of antimicrobial treatment should be individualised and tailored to the clinical response of the patient [71]. Therefore, it should be withdrawn, as soon as possible, once the symptoms of infection are controlled [65]. Table 3 includes general recommendations of duration of antimicrobial treatment in LRTs.

7.- SELECT THE ANTIBIOTIC WITH THE LEAST ANTIMICROBIAL RESISTANCE DEVELOPMENT AND ECOLOGICAL EFFECTS

The use of antimicrobials should minimise the development of resistance as much as possible. This is achieved with antimicrobials with high bacterial eradication capacity and with treatment schemes that ensure effective concentrations at the focus of infection that exceed the so-called mutant prevention concentration (MPC) that prevents microorganisms from entering in the window of selection [72,73]. Also with those that allow to reduce at maximum level the bacterial inoculum at the focus of infection. Treatment with amoxicillin (2 g/12 h), cefditoren (400 mg/12 h) or levofloxacin (500 mg/12 h) has a lower risk of selecting for resistance in *S. pneumoniae* than with lower doses of amoxicillin (875/8 h) or levofloxacin (500 mg/12 h) or with the macrolides or the oral cephalosporins cefuroxime (500 mg/12 h) or cefixime (400 mg/12 h) [4,74] (Figure 3).

Furthermore, regardless of resistance, the antimicrobial chosen must avoid ecological damage to the normal microbiota. This occurs with antimicrobials that do not reduce the so-called "colonisation resistance", a property for which the normal microbiota persists over time on its normal niche despite external aggression or disturbance and also named resiliency. This is generally produced with antimicrobials with minimum or null effect on anaerobic microbiota which are normally those that prevent colonisation of mucosal surfaces with multidrug-resistant bacteria. Several studies have shown that cephalosporins, including those administered by oral route, or amoxicillin have less ecological impact than fluoroquinolones, clindamycin or macrolides, with the usual microbiota recovering more quickly than with the former [75-77]. Fluoroquinolones also have a greater effect on the development of *Clostridioides difficile* infection than penicillins or cephalosporins [78,79].

8.- ROTATION AND DIVERSIFICATION OF ANTIMICROBIALS

Antibiotic rotation, understood as the suspension of the use of antimicrobial agents for a certain period of time to be reintroduced later, is not a new concept. It has been used in different clinical settings since the 1950s as one of the strategies proposed to control the emergence of antimicrobial resistance, reduce infection rates or reduce antimicrobial consumption [80,81]. This approach aims to reduce the exposure time of bacteria to an antibiotic and thus reduce the selective pressure it exerts on the microbiota of the individual, minimising the emergence of resistance. Several studies have shown that this method is particularly useful in certain clinical departments or patient settings where there is a high use of antimicrobials [82].

On the other hand, diversifying the use of antimicrobials has also been shown to be effective in reducing the emergence and reduction of resistance [83].

In the case of COPD treatment, both strategies are critical

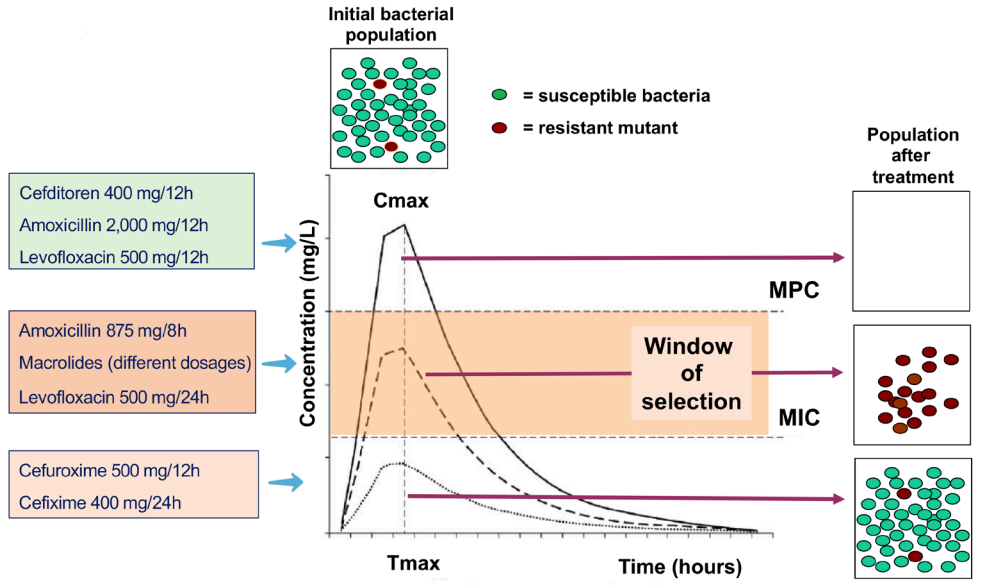

Figure 3 Representation of minimal inhibitory concentration (CMI), mutant selection window and mutant prevention concentration (MPC) over a pharmacokinetic curve of an antimicrobial administered orally and different antimicrobials used in *S. pneumoniae* respiratory tract infections achieving different concentrations [modified from references 4 and 73]

to resolve exacerbations. Antimicrobial rotation should include the antimicrobials with most eradication property, so that it effectively contributes to reduce the risk of selection of resistance by decreasing the bacterial burden (quantitative "fall and rise" theory) [6]. It is important to identify the most appropriate antibiotic groups to be rotated in our geographic area, which may vary from one area to another depending on resistance rates. The sequences to be followed in the rotations and the time that should elapse between rotations should also be defined at local level.

In CAP, diversification in antibiotic treatment avoids exerting a high selection pressure and thus spreading strains resistant to that antibiotic [6]. This requires close epidemiological surveillance in the different work settings and insistence on shortening the duration of empirical treatments according to clinical guidelines to reduce antibiotic pressure globally.

9.- SWITCH TO THE ORAL ROUTE AS SOON AS POSSIBLE

The advantages of implementing sequential therapy are the reduction of antimicrobial treatment costs, the reduced need for accessories and devices for the preparation and administration of the drug (needles, infusion sets, syringes, intravenous solutions, etc), providing the patient with greater comfort, mobility and independence, reducing complications by decreasing the frequency of adverse effects related to intravenous administration, mainly phlebitis and nosocomial infection associated with this route (secondary bacteraemia, septic phlebitis), avoiding the possibility of contracting any type of nosocomial infection associated with a long hospital stay and reducing hospital stay [84,85].

The criteria that patients must meet to proceed with the switch to oral formulation are: heart rate <100 bpm, respiratory rate <24 rpm, axillary temperature below 37.2°C, systolic blood pressure >90 mmHg, oxygen saturation >90%, good level of consciousness and tolerance to the oral route [86].Regarding the selection of the appropriate oral antimicrobial, this should be done in the same way as the intravenous depending on the possible expected aetiology (causative microorganism), local sensitivity and resistance patterns, PK/PD characteristics of each antibiotic and the epidemiological situations and particular characteristics of the patient (age, comorbidity, contraindications, allergic history, etc.).

Table 4 shows the equivalence of antimicrobials for establishing sequential therapy in patients with COPD exacerbations or CAP. In the case of amoxicillin-clavulanic acid and fluoroquinolones, there are galenic presentations of the same antibiotic for both routes. However, in the case of amoxicillin-clavulanic acid, it should be considered that the change from intravenous dosing to the available oral formulation (875mg/125mg) implies a decrease in the dose of amoxicillin, which would fall within the mutant selection window, and an increase in clavulanic acid, so it may also be appropriate to perform sequential therapy with another beta-lactam such as cefditoren. In the case of third generation intravenous cepha-

Table 4 Equivalence of antimicrobials for sequential therapy in patients with COPD exacerbations or CAP

Intravenous treatment	Oral treatment
Amoxicillin-clavulanate	Amoxicillin-clavulanate or cefditoren
Fluoroquinolone	Fluoroquinolones
Macrolides	Macrolides
Cefotaxime or ceftriaxone	Cefditoren

losporins, the most appropriate sequential therapy is cefditoren due to the fact that it has a similar spectrum and intrinsic activity [4].

10.- KEEPING UP TO DATE: CONSULT THE ANTIMICROBIAL TREATMENT GUIDELINES

Along with proven experience and practical common sense, knowledge based on scientific evidence is a third key element in the competence of healthcare and/or research doctors. They must try to keep up to date with scientific knowledge. The increased volume of information, together with the changing dynamism of the results of studies and trials, and their interpretations, makes difficult to manage the acquisition and assimilation of knowledge. In addition to the modern and fragile express assertions of a multitude of social networks, a more rigorous and controlled way is to consult clinical practice guidelines, consensus documents and recommendations made by methodologists and experts in each subject under the umbrella of official agencies or scientific societies.

The objectives of a clinical guideline, such as those on LRTIs, should be to improve the appropriateness of empirical antibiotic treatment, reduce uncertainty and medical errors, assist in decision-making, improve adherence to protocols, reduce and optimise the use of antimicrobials, allow for shorter treatment durations and/or stays, help control the selection of resistant bacteria and reduce costs. Other functions that an international, national or local guidelines may include are serving as a reference standard or criterion for quality and appropriateness of treatments in programmes for antimicrobial stewardship, keeping knowledge up to date by compiling new evidence on the approach to infections (diagnostic criteria, pharmacological and non-pharmacological recommendations according to patient characteristics and severity of the process. Moreover, they are tools for shared decision-making with the patient and for training activities.

The guidelines must be constantly updated, consult the appropriate sources, rigorously analyse the results of the studies selected and evaluated, and offer comparative exposition of these results with respect to the considered recommendations that will be offered in the guideline. Failure to do so may result in the opposite ending with outdated antibiotic treatment indications that do not include all available options, that do not establish appropriate dosages and precise duration of treatment, or that even show doubt or confusion.

In the case of guidelines for the selection of oral antibiotics in LRTIs, in addition to international guidelines, there are good and sufficient national guidelines and expert documents available in Spain [4-8,20,16,30-35,87-89]. In these ones, we have indications for antimicrobial treatment in two major respiratory infectious syndromes: exacerbation of COPD and outpatient CAP. For both entities, a classification is established from mild to severe, or risk factors for specific microorganisms that require a more special or selected antimicrobial therapy (e.g. of *P. aeruginosa*) or by age and underlying comorbidities. Based on this, different scenarios or risk factors are cross-referenced with the main microorganisms causing infection, priority indications for empirical antibiotic treatment are given and other alternative options are listed (Table 5) [34].

In turn, with regard to the antibiotics available and recommended for the oral treatment of LRTIs, the guidelines show which antibiotics are available, to which class or families they belong, their spectrum of microorganisms included according to their mechanism of action and intrinsic activity and, of course, comparative assessments are established in relevant aspects such as safety and tolerance, drug interactions and risk of dysbiosis due to alteration of the microbiome, all translated in a practical way, for example, into the risk of causing infection by *C. difficile*.

Of the classes of antimicrobials included and assessed in these guidelines, for classical respiratory bacterial pathogens (such as *S. pneumoniae, H. influenzae* and *M. catarrhalis*), the beta-lactam family stands out especially in their indication, distancing them from the fluoroquinolone family for several reasons, one of them being the safety, tolerance and pharmacological interactions, with a better profile for the former and with pharmacological alerts indicating toxicity problems and complications with the latter.

However, not all beta-lactams have the same characteristics and behave in the same way, and some of the guidelines go so far as to comparatively dissect the different oral options in this family: aminopenicillin and beta-lactamase inhibitor combination (such as amoxicillin-clavulanic acid) or second (cefuroxime axetil) and third generation cephalosporins (cefixime and cefditoren). In turn, clear differences can be established between the cephalosporins themselves, as some of them may show a lack of sufficient or optimal intrinsic activity against Gram-positive microorganisms (pneumococci), as is the case for cefixime or ceftibuten, or offer only a deficient and suboptimal concentration achieved in the lung at the dose marketed or indicated in the summary of product characteristics (such as cefuroxime), making some of these beta-lactam options less advisable than other third-generation oral cephalosporins (cefditoren), which are more recommended for community respiratory pathology.

In addition, not all guidelines include other relevant as-

Table 5 | **Oral antimicrobials recommended in mild or moderate COPD exacerbations and community acquired pneumonia [34]**

		Empiric antibiotics*	
	Microorganisms	First choice	Alternative
COPD exacerbation (COPD-E)			
Mild	*H. influenzae* *S. pneumoniae* *M. catarrhalis*	Amoxicillin-clavulanate 875-125mg/8h 5-7 days Cefditoren[a] 400 mg/12h, 5 days	Levofloxacin[c] 500mg/24 h, 5-7 days Moxifloxacin[c] 400mg/24 h, 5-7 days
Moderate without risk factors for *P. aeruginosa*	*H. influenzae* *S. pneumoniae* *M. catarrhalis* + Pen-R *S. pneumoniae*	Amoxicillin-clavulanate 875-125mg/8h 5-7 days Cefditoren[a] 400 mg/12h, 5 days	Levofloxacin[c] 500mg/24h, 5-7 days Moxifloxacin[c] 400mg/d, 5-7 days
Moderate with risk factors for *P. aeruginosa*	*P. aeruginosa*	Ciprofloxacin 750 mg/12h, 5-7 days Levofloxacin 500 mg/12h, 5-7 days	
Community acquired pneumonia (CAP)			
Non severe CAP in <65 years, without significant chronic morbidity or without risk factors for infection with Gram-negatives or *Legionella* spp, irrespective of aetiological suspicion	*S. pneumoniae* *H. influenzae* *M. pneumoniae*	Amoxicillin 1g/8h, 5-7 days	Cefditoren[a] 400mg/12h, 5 days Levofloxacin[c] 500mg/d, 5-7days Moxifloxacin[c] 400mg/d, 5-7 days
Non severe CAP in <65 years, with significant chronic morbidity or other risk factors for infection with Gram-negatives	*S. pneumoniae* *H. influenzae* *K. pneumoniae* / other enterobacterial *Legionella* spp	Amoxicillin-clavulanic 875-125 mg/8h 5-7 days + macrolide[b] Cefditoren[a] 400mg/12h, 5 días +/- macrolide[b]	Levofloxacin[c] 500mg/d, 5-7días Moxifloxacin[c] 400mg/d, 5-7 días
CAP in COPD	*S. pneumoniae* *H. influenzae* *M. pneumoniae*	Amoxicilin-clavulanate 875-125 mg/8h 5-7 days +/- macrolide[b] Cefditoren[a] 400mg/12h, 5 días	

***Dosing regimen correspond to current Spanish recommendations included in the guidelines and not that included in the summary of product characteristics:**

[a]It should be prescribed if there is documented penicillin allergy or if the patient has been previously treated with amoxicillin or amoxicillin-clavulanate

[b]Add a macrolide (azithromycin 500 mg/24 h, 3 days or clarithromycin 500 mg/12, 7 days) if there are risk factor or suspicion of *L. pneumophila* infection

[c]Only recommended when a macrolide is not possible

pects, such as: a) some third-generation oral cephalosporins with sufficient intrinsic activity against the most common respiratory pathogens, with comfortable dosage and good safety profile (e.g. cefditoren) are considered first line treatment option, particularly in patients older than 65 years. Moreover, it should be prescribed if a course of treatment with amoxicillin or amoxicillin-clavulanic acid has been used in the previous three months; b) the addition of a macrolide (azithromycin 500 mg/day, oral for three days or clarithromycin 500 mg/12h for seven days) should be considered if there are epidemiological risk factors or clinical suspicions of acquiring and developing infection with *L. pneumophila* or other "atypical" microorganisms and cannot be ruled out by rapid microbiological tests and c) use of fluoroquinolones only when beta-lactams cannot be used or when there is a need to cover certain microorganisms such as Gram-negative bacilli with resistance mechanisms, e.g. *P. aeruginosa*.

Finally, the inclusion of a given antimicrobial family globally or an antibiotic in particular in an oral antibiotic treatment guideline for LRTIs should be made on the basis of good tolerance profile, low capacity for selection of resistance mechanisms and minimal ecological impact, even assuming equal efficacy. Overall, beta-lactams have these characteristics and exceed the fluoroquinolone family in efficacy and tolerance, which are included as alternatives in LRTI guidelines and which have safety alerts by regulatory agencies [54,55]. The inclusion in these guidelines of certain third-generation oral cephalosporins, such as ceftditoren, with high efficacy and recognised tolerance, since they are not all the same, also helps to diversify the use of antibiotics, one of the pillars to minimise the selection of resistant and multiresistant bacteria. This is a key objective in the programmes to combat antimicrobial resistance and antimicrobial stewardship.

CONCLUSIONS

The selection of oral antibiotics in LRTI should be based on knowledge of the bacterial aetiology and the frequency of local antimicrobial resistance, preferably those with a rapid mode of action, which achieve the greatest effect in the shortest time and with the fewest adverse effects (toxicity, interactions, resistance and/or ecological impact). Whenever possible, rotate and diversify antimicrobials and switch to the oral route as soon as possible. This Decalogue is intended as an aid to prescribing oral treatment for mild to moderate exacerbations of COPD and CAP. The concepts contained in this Decalogue are also contemplate in clinical treatment guideless.

CONFLICTS OF INTEREST

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