Introduction
Since their discovery in the 1930s and until the 1980s, it was generally believed that antibiotics were capable of curing almost all bacterial infections. More recently, the appearance of increasing resistance to antibiotics and the emergence of multiresistant microorganisms have given rise to growing concern among physicians, and that concern has now started to filter through to society in general. The problem is further aggravated by a situation that not many people are currently aware of, that is, the limited prospects for future development of new antibiotics in the short to medium term. Appropriate use of available antibiotics based on a thorough understanding of their in vivo activity and the emergence of new forms of administration, such as inhalers, may help to alleviate the problem.

Microorganisms Continue to Develop Resistance
The following examples may be useful. In the early 1990s, the prevalence in hospitals of methicillin-resistant Staphylococcus aureus (MRSA) was around 5% and staphylococcal infections could be treated successfully with methicillin and its derivatives or first- and second-generation cephalosporins.1 Today, in hospitals in the United States of America, 50% to 60% of the S. aureus strains colonizing or infecting patients are resistant to methicillin and by extension to oxacillin, cloxacillin, amoxicillin–clavulanic acid, and the fluoroquinolones.2 As if this were not bad enough, cases have now been reported of infections resistant to vancomycin, the first-line treatment for MRSA.4 In Spain, although considerable geographical variation exists, the last 11 years have seen an overall increase in MRSA isolates, both nosocomial (from 22% to 41%) and community-acquired (from 7% to 28%).3 Although to date MRSA has primarily been a major problem affecting hospitals, in recent years there have been reports of this pathogen causing serious respiratory and skin infections in previously healthy young people with no history of contact with hospital or institutional settings; this development has caused great concern among epidemiologists.5

Infections caused by extended-spectrum β-lactamase-producing gram-negative bacteria (in particular Klebsiella pneumoniae and Escherichia coli) resistant to cephalosporins and other β-lactam antibiotics are occurring with ever greater frequency in hospitals and

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The primary impact of the worrying increase in resistance among anaerobes, and in particular the *Bacteroides fragilis* group, is on the management of intra-abdominal and pelvic infections. However, the emergence of resistant strains of anaerobic microorganisms previously considered highly susceptible to antibiotics, such as *Peptostreptococcus* species, may have repercussions on infectious respiratory diseases, including community-acquired infections.10

The situation of *Haemophilus influenzae* is of greater importance for respiratory infections and in particular chronic obstructive pulmonary disease (COPD). The development of resistance to amoxicillin through production of β-lactamas has been well known for some time, and such strains now represent over 25% of those isolated in Spain. The fact that almost 5% of the non-β-lactamase-producing *H influenzae* strains are also amoxicillin-resistant is less well known.11 Fortunately, the prevalence of strains resistant to amoxicillin–clavulanic acid, whether β-lactamase producing or not, is much lower. It has recently been reported that the incidence in Japan of *H influenzae* strains resistant to amoxicillin–clavulanic acid and first- and second-generation cephalosporins mediated by mutations in target proteins (penicillin-binding proteins) has increased to high levels in recent years and now exceeds 40%,2 raising the question of whether this may be an emerging problem in the world as a whole. In Spain, amoxicillin–clavulanic acid, and particularly the sustained-release formulation (2000/125 mg), is still effective against practically all non-β-lactamase-producing strains of *H influenzae* with a pharmacodynamic profile, similar to that of clarithromycin and azithromycin, the only macrolides having in vitro activity against the pneumococcus, particularly most of the oral cephalosporins (including cefaclor, cefixime, cefuroxime, and cefuroxime axetil), which should not be used in cases where pneumococcal infection a possibility. Moreover, as would seem logical in the context of an antibiotic with low activity against the pneumococcus, the emergence of strains highly resistant to β-lactams has been associated with the prescription in outpatient settings of first- and second-generation oral cephalosporins rather than with the use of other penicillins and cephalosporins.7,8

However, in vitro resistance to macrolides, which amply exceeds 30% in Spain (50% among children), does have important practical implications. This is because in most cases in Spain amoxicillin–clavulanic acid is the only available antibiotic that is effective against the pneumococcus, especially in CAP.17 Also make the s(CAP) led to the recommendation to use macrolides as the first line therapy in the treatment of CAP and other types of respiratory tract infections and widespread prescription of macrolides, especially the long-acting formulations with administration once or twice daily,3 has given rise all over the world to the rapid emergence of pneumococcal strains resistant to these antibiotics, a development with a much greater impact on the clinical management of respiratory infections than in vitro resistance to β-lactam antibiotics. In effect, there is abundant evidence in the literature that a β-lactam agent with good activity against *S pneumoniae* (such as amoxicillin or cefotaxime/ceftriaxone) prescribed at adequate doses in clinical practice is adequate for controlling a nonmeningeal pneumococcal infection in the immense majority of cases even when the causative pathogen has displayed resistance in the laboratory.3,10,22

The pharmacokinetically enhanced behavior of the new sustained-release formulations of amoxicillin has increased the activity of this agent.17-20 This does not, however, apply to the other β-lactam antibiotics that are commercially available and widely prescribed. Many of these agents have low activity against the pneumococcus, particularly most of the oral cephalosporins (including cefaclor, cefixime, cefuroxime, and cefuroxime axetil), which should not be used in cases where pneumococcal infection a possibility. Moreover, as would seem logical in the context of an antibiotic with low activity against the pneumococcus, the emergence of strains highly resistant to β-lactams has been associated with the prescription in outpatient settings of first- and second-generation oral cephalosporins rather than with the use of other penicillins and cephalosporins.7,8 This situation has been highlighted by published reports of clinical failures after macrolide treatment that contrast with the outcomes obtained using β-lactam antibiotics effective against *S pneumoniae*.11-14 Consequently, monotherapy with macrolides is not recommended for the treatment of infections that may be pneumococcal, especially in CAP.17 Also make the s(CAP) led to the recommendation to use macrolides as the first line therapy in the treatment of CAP and other types of respiratory tract infections and widespread prescription of macrolides.
resistance to fluorquinolones, it is worth noting that in contradictory data on the emergence of pneumococcal year, make the future of this once promising antibiotic levofloxacin in some areas of the country to as high as from 3.2% of strains with reduced susceptibility to The published figures for Spain vary considerably, ranging 9% in others. Although the literature includes some enzyme occurs relatively easily, resulting in complete resistance that gives rise to treatment failures, which probably already exceed 20% of cases. The prevalence of strains that have already undergone a single mutation but are still susceptible in vitro is not known with any precision because the data available are contradictory. However, it is certain that, like all other antibiotics, it is directly related to their consumption and, uniquely, to the community environment. It was recently confirmed that of all the classes of antibiotics used to treat pneumococcal infections (including the β-lactam antibiotics, macrolides, and aminoglycosides) the quinolones played the most important role in the generation of resistance within 3 months of their use. Ciprofloxacin has poor activity against S. pneumoniae and will therefore exert a stronger selective pressure for the generation of resistant strains, both reasons why this antibiotic should not be used in infections presumed to be pneumococcal. Moxifloxacin, in contrast, displays the highest intrinsic potency against S. pneumoniae, and this greatly reduces the risk of it inducing resistance to fluorquinolones. Respiratory fluorquinolones are exceptional antimicrobial agents, and this is precisely one of the reasons we have an obligation to preserve them through responsible use, especially in the outpatient setting. The Centers for Disease Control and Prevention recommend limiting the use of fluorquinolones to certain patients and situations, which include patients allergic to alternatives, those in whom treatment with β-lactam antibiotics has failed, and infections demonstrated or strongly suspected to be due to a drug-resistant pneumococcus.

To minimize the possibility of treatment failure due to resistance acquired during a recent course of treatment, some authors advocate constriction of specific antibiotic regimens in each patient.

With Very Few New Antibiotics in Development We Have No Reserve

The development of a new antibiotic represents a considerable investment that does not always give results. It takes approximately 10 years to establish the efficacy and safety of new compounds. This means that the large multinational pharmaceutical companies have a greater interest in researching drugs to treat highly prevalent diseases requiring prolonged, sometimes lifelong, treatments (hypertension, lipid metabolic disorder, etc) rather than short and intermittent courses of treatment, as is the case with antibiotics. As a result, the large companies have by and large given up researching and investing in new antibiotics that would represent an improvement over those currently on the market. Some facts and figures on this subject are very revealing. Between 1983 and 2002, the number of antimicrobial agents approved declined by 50% over previous years, and in 2004, only 10 of the 118 new drugs approved by the American Food and Drug Administration were antibiotics. Most of the new antimicrobial agents (linezolid, daptomycin) are the target resistant gram-positive bacilli, particularly MRSA, while others are more adapted to community-acquired respiratory infections treated in an outpatient (telithromycin, ceftoloren)
strains of the is not yet known, a growing body of information is available for CAP, nosocomial pneumonia, and COPD exacerbations. While the optimum duration of antibiotic therapy short course antibiotic treatment of lower respiratory system fortunately been a steady shift towards more energetic second-generation cephalosporins. Moreover, there has progressive reduction in the use of the antibiotics likely resistant strains. This is accompanied by a corresponding and minimize the selective pressure for the generation of antibiotics, which facilitate more rapid bacterial eradication and we are more clearly identifying the most active pharmacodynamic parameters are coming onto the market. Finally, high dosage formulas with more favorable pharmacokinetic and pharmacodynamic profiles of each drug.

The increase in antimicrobial resistance and the precarious outlook for the development of new antibiotics in the foreseeable future, it is essential to carry out a meticulous review of the antibiotics currently available if we are to obtain the best results with them. In fact, with the exception of the fluoroquinolones, we are already witnessing a decline in the global use of antibiotics.

Bacterial Eradication. The Importance of Pharmacokinetics and Pharmacodynamics (Figure 1)

It is generally understood that curing certain infections, such as endocarditis, meningitis, and osteomyelitis, necessarily requires eradication of the causative bacteria. In the case of respiratory infections, however, eradication has traditionally been considered a secondary objective subsidiary to the primary aim of clinical efficacy. This is due to a series of factors, including the high spontaneous cure rate in certain community-acquired respiratory infections, a phenomenon that makes it difficult to distinguish between very effective antibiotics and other less effective agents and also on occasion gives rise to poor linear correlation between eradication rates and clinical cure, due in part to the presence of viral infections.

As a result, if we measure the efficacy of an antibiotic on the basis of improvement in symptoms, some very effective
drugs may not appear particularly effective and others with poorer activity may appear better than they actually are. In COPD, the situation is even more complicated because some of these patients are colonized with potentially pathogenic bacteria, and it is often impossible to differentiate between colonization and infection and to achieve bacterial eradication. Logically, however, and in spite of these difficulties, there is a growing body of evidence that bacterial eradication plays a very important role in the achievement of a favorable clinical response, the rapid resolution of symptoms, and in reducing both the number of relapses and the selective pressure for resistance.64-67 It is important to always bear in mind that the number of resistant populations in the host, who may survive at the site of infection and in the nasopharynx of carriers will re-colonize the mucosal membranes once antibiotic treatment is discontinued, thereby increasing the number of resistant populations in the host, who may in turn transmit these antibiotic-resistant clones to the rest of the population.64,66 Consequently, bacterial eradication as near as possible to 100% has an additional advantage, apart from clinical efficacy, in that it minimizes the risk of the bacteria developing resistance in vivo during treatment. Pharmacodynamic parameters predict bacterial eradication and vary from one antibiotic to another. The pharmacodynamic and pharmacokinetic profiles of antibiotics enable us to predict the drug’s antibacterial effect and, consequently, the clinical results, the appropriate dose regimen, and the likelihood that resistance will develop. Antibiotic activity against a specific bacteria has traditionally been assessed in vitro by measurement of the minimum inhibitory concentration (MIC) using the MIC value (the concentration necessary to inhibit the growth of 90% of a bacterial strain); hence the lower the MIC, the greater the antimicrobial activity. Although this is undoubtedly a very important parameter, it is even more important to predict as accurately as possible what will happen in the patient and at the site of the bacterial infection when a specific dose of the antibiotic in question is administered. Pharmacokinetics is essentially concerned with the factors (absorption, distribution, metabolism, and elimination) that, in combination with the dosage regimen, determine the time course of drug concentrations in serum and tissues. Pharmacodynamics deals with the relationship between the concentration of the antibiotic in the body and its antibacterial activity against a particular organism, taking into account the MIC of the antibiotic for the bacterial strain in question.68,69

As is well known, antibiotics can be divided into 2 major categories on the basis of the activity and duration of their effect. Time-dependent antibiotics, a group that includes the β-lactams and the macrolides, are more effective the longer concentrations above the MIC (albeit only slightly) can be maintained. A β-lactam or macrolide is thought to have guaranteed efficacy if the concentration of free (not protein bound) drug at the site of infection is at least 4 times the MIC.70-72 A β-lactam antibiotic with a long half-life.73 An example of a drug with a good pharmacodynamic profile is the sustained-release oral formulation of amoxicillin-clavulanic acid (2000-125mg), which is more effective than conventional formulations.74,75 The period during which the antibiotic concentration remains above the MIC is particularly crucial in antibiotics—such as the β-lactams—that have no postantibiotic effect (defined as an antimicrobial effect that persists even after complete removal of the drug from the site of infection). In the other large category of antibiotics, activity is concentration-dependent rather than time-dependent, so that, in general terms, a higher dose equates with greater activity. The activity of some of these agents, such as the aminoglycosides, depends essentially on the peak concentration, such that the higher the peak concentration achieved the greater the efficacy with respect to the susceptibility of the pathogen; the general consensus is that the peak concentration should be 10 to 12 times the MIC. These antibiotics should, therefore, be administered in high doses (5-7 mg/kg for gentamicin or tobramycin and 15-20 mg/kg for amikacin) once a day for 30 to 60 minutes and the complete course need not exceed 3 to 5 days. Under these conditions, the single dose affords more rapid bactericidal activity, a greater postantibiotic effect, and less selective pressure for the generation of resistant strains. The first dose is particularly important because the possibility of curing the infection will be 80% to 100% if it achieves a peak concentration 10 to 15 times the MIC.68-69

In the case of other concentration-dependent antibiotics, such as the fluoroquinolones, azalides, and ketolids, the ratio of the antibiotic area under the concentration-time curve (AUC) to the organism’s MIC for this drug (AUC/MIC) is the best predictor of both clinical efficacy and bacterial eradication. The activity of these antibiotics is related to overall exposure and depends on both the peak concentration achieved and the length of time this concentration remains above the MIC (a result that will depend largely on the half-life of the drug). In order to prevent a fluoroquinolone from inducing resistance, a drug concentration at least 8 times the MIC should be achieved and maintained long enough (usually between 4 and 6 hours) to eliminate potential mutants with a high MIC.68 It is, therefore, advisable to use ciprofloxacin to treat infections presumed to be pneumococcal.74 A better treatment option for such infections is a 750 mg dose of oral levofloxacin every 24 hours, a dose formulation available in other countries. If moxifloxacin is used, a 400 mg dose every 24 hours is adequate because this drug has a longer half-life and a lower MIC for S pneumoniae. For the oral treatment of infections due to P aeruginosa we can use 750 mg of ciprofloxacin or 500 mg of levofloxacin, both at 12 hour intervals. The novel 2 g formulation of azithromycin provides a complete treatment for CAP in a single dose.76,77 Correct practical application of pharmacokinetic and pharmacodynamic concepts can provide numerous
advantages, including improved treatment efficacy, shorter courses of treatment, better treatment options for outpatient settings, and a reduced incidence of resistance.83,108

Inhaled and Immunomodulatory Antibiotics in the Treatment of Respiratory Infections

The use of antibiotic administration routes not commonly used in standard practice has been documented in patients with cystic fibrosis.107-126 Particularly interesting is the treatment of infections caused by *P. aeruginosa*. The benefits demonstrated in these studies indicate that treatment with inhaled antibiotics is associated with a significant improvement in clinical and functional parameters, and achieves a significant reduction in bacterial load in sputum and, in some patients, complete eradication of the target pathogen. Inhaled treatment also reduced the frequency of hospital admission, the number of hospital stays, and the patients’ quality of life. Given the good results obtained in these patients, the use of inhaled antibiotics is gradually being extended to forms of bronchiectasis other than cystic fibrosis for the treatment of chronic *P. aeruginosa* infection.127,134

Given the appearance of evidence that appears to support good results using this route of administration, and taking into account that very high concentrations of antibiotic in sputum are achieved (25 times the MIC, with a mean serum/sputum concentration of 0.01), that systemic absorption is slight, and that important adverse effects are uncommon, it would appear reasonable to suggest that this route of administration could open the door to new therapeutic options in the treatment of chronic respiratory infections. In a very recent study that compared ex-smokers with stable COPD, ex-smokers without COPD, and healthy nonsmokers, Sethi et al147 found colonization to be an important cause of inflammation even in COPD patients who were no longer active smokers, and made the point that it may contribute to progression of the disease. One very important aspect of this study was the use of bronchoalveolar lavage rather than sputum, which facilitated study of the small airway, a key area in COPD patients. The importance of colonization in COPD and other respiratory diseases should stimulate the search for new therapeutic approaches. In this context, effective vaccines could obviously be a fundamental tool, but it would certainly also be very interesting to have large studies evaluating the effectiveness of treatment with inhaled antibiotics.

Another option that must be studied is the possible usefulness of macrolides with 14 or 15 atoms of the guidelines to achieve early stability in our patients,148 We must ask ourselves whether we are making proper use and whether we are properly using and recommending the antibiotics appropriately.85-86

In conclusion we can say that at this time the increase in bacterial resistance to antibiotics clearly outstrips the prospects of new antibiotic development in the short to medium term. We must therefore combat respiratory infections on the basis of clinical strategies and rigorous guidelines, and this will often imply modifying our strategies for treating infections. We will always have to prescribe drugs that are not only effective but also exert the least selective pressure. We must avoid supoptimal doses and unjustifiably prolonged courses of treatment, educate the population against self-prescription and failure to complete treatment, and also improve our understanding of the pharmacokinetics and pharmacodynamics of the different drugs and develop vaccines effective against the most important respiratory pathogens. The site of the battlefield is also clear: outpatient medicine and, particularly, primary care settings, where infection is the primary motive for consultation and where 80% to 95% of antibiotic consumption is prescribed, 80% of which are prescribed to treat respiratory infections. The primary care setting is where the immense majority of resistances originate. We must ask ourselves whether we are making proper use of the guidelines to achieve early stability in our patients, and whether we are properly using and recommending the available influenza and pneumococcal vaccinations that have been shown to reduce both antibiotic consumption and frequency of infection with resistant strains in children and older patients. We should commit ourselves to the fight against the self-perpetuating cycle of antibiotic resistance.
The future is in our hands.

and eventually even greater antibiotic pressure (Figure 2).

10. Hetch DW. Prevalence of antibiotic resistance in anaerobic bacteria: \(450-9\)


2. Centers for Disease Control and Prevention (CDC). Vancomycin-resistant \(450-9\)


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pressure creating resistance that leads to clinical failure and eventually even greater antibiotic pressure (Figure 2).
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