REVIEW

Will We Still Have Antibiotics Tomorrow?

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Since the discovery of antibiotics, it has been generally believed that these antimicrobials are 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.

Key words: *Antibiotics. Respiratory infection. Resistance.*

¿Seguiremos teniendo antibióticos mañana?

Desde el descubrimiento de los antibióticos se tenía la creencia generalizada de que eran capaces de curar casi la totalidad de las infecciones bacterianas. Desde entonces, la aparición y el incremento de resistencias a los antimicrobianos y la constatación de la emergencia de microorganismos multirresistentes han generado entre los médicos una preocupación creciente, que empieza a trascender a la sociedad. La escasa perspectiva de desarrollo de nuevos fármacos antibióticos a corto-medio plazo es poco conocida y agrava el problema. El aprovechamiento de los antibióticos disponibles, mediante el conocimiento en profundidad de su actividad in vivo, así como la emergencia de nuevas formas de administración como la inhalada, puede ayudar a paliar el problema.

Palabras clave: *Antibióticos. Infección respiratoria. Resistencias.*

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. Since the 1980s, however, the steady increase in resistance to antibiotics and the emergence of multiresistant microorganisms has been a cause for growing concern among physicians, and that concern has now started to filter through to society in general. Moreover, the true magnitude of this problem only becomes clear when it is seen in the context of a situation that not many people, even doctors, are currently aware of, that is, the limited prospects for future development of new antibiotics in the short to medium term.

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. 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.[1] As if this were not bad enough, cases have now been reported of infections resistant to vancomycin, the first-line treatment for MRSA.[2] 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[4]; 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

institutional settings, both in isolated cases and epidemic outbreaks.[6] These infections, which may affect the respiratory system, the abdominal organs, soft tissues, skin, or the urinary tract, are associated with a high mortality rate. Several risk factors have been identified, including older age, diabetes and other comorbidities, hospitalization, residence in an institution, and prior administration of antibiotics, particularly second- and third-generation cephalosporins and fluoroquinolones.[7,8] Although these infections have until now been almost exclusively limited to institutional settings—where control programs should be as strict as possible and include barrier measures and judicious use of antibiotics—it is very likely that we will see a growing trend in the future towards spread to outpatients.[8,9]

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-lactamases has been well known for some time, and such strains now represent over 25% of those isolated in sputum 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 with resistance 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%,[12] raising the question of whether this may be an emerging problem in the rest of the world. In Spain, amoxicillin–clavulanic acid, and particularly the sustained-release formulation (2000/125 mg), is still effective against practically all strains of *H influenzae*, as are ciprofloxacin, levofloxacin, moxifloxacin, and the new third-generation oral cephalosporin cefditoren. Cefuroxime, despite producing good sensitivity results in vitro, has a clearly inferior pharmacodynamic profile, similar to that of clarithromycin and azithromycin, the only macrolides having in vitro activity against *H influenzae* with a pharmacodynamic sensitivity between 60% and 65%.[11,13] The in vitro susceptibility of *Moraxella catarrhalis*, the third most common pathogen after *Streptococcus pneumoniae* and *H influenzae* in COPD exacerbations, is low for amoxicillin because of its high levels of β-lactamase production. However, like *H influenzae*, this pathogen has an in vitro susceptibility of almost 100% for amoxicillin–clavulanic acid, cefuroxime, ciprofloxacin, moxifloxacin, levofloxacin, and cefditoren.[11,14-16]

Pneumococcus, the Ever Present Battle Horse

Since the early 1990s, there has been a widespread awareness of the loss of activity among β-lactam antibiotics in inhibiting the growth in the laboratory of a large percentage of *S pneumoniae* strains due to a variable reduction in the affinity of the target penicillin-binding proteins in the bacteria for these antibiotics. This development, together with the emergence of *Legionella pneumophila* as a cause of life-threatening community-acquired pneumonia (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. Widespread prescription of macrolides, especially the long-acting formulations with administration once or twice daily,[17] 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 capable of controlling a nonmeningeal pneumococcal infection in the immense majority of cases even when the causative pathogen has displayed resistance in the laboratory.[18-22] The pharmacokinetically enhanced behavior of the new sustained-release formulations of amoxicillin has increased the activity of this agent.[23-25]

This does not, however, apply to the other β-lactam antibiotics that are commercially available and widely prescribed. Many of these agents have lower activity against the pneumococcus, particularly most of the oral cephalosporins (including cefaclor, cefixime, cefibuten, cefpodoxime, and cefuroxime), 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.[17]

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 resistance is due to mutations in the target bacterial ribosome, such that the macrolide concentrations necessary to sustain efficacy are would be unattainable. 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*.[21,26-30] Consequently, monotherapy with macrolides is not recommended for the treatment of infections that may be pneumococcal, especially in CAP.[31] Also unlike the situation found with the β-lactam antibiotics, pneumococcal resistance to one macrolide is associated with cross-resistance to the other antimicrobials in this class and to clindamycin. When it

appeared, telithromycin, an erythromycin-derived ketolide that recovered the efficacy of macrolides against pneumococcal strains that had developed resistance to this group of drugs,[32,33] raised considerable interest and was included in the guidelines as a first line treatment for CAP in outpatients.[31] However, subsequent reports of cases of severe liver toxicity, worsening of myasthenia gravis, and the appearance of adverse effects affecting vision and level of consciousness led the main regulatory agencies—the European Medicines Agency and the US Food and Drug Administration—to restrict and withdraw, respectively, approval for use in sinusitis, bronchitis, and COPD exacerbations.[34,35] These decisions, which were taken this year, make the future of this once promising antibiotic very uncertain.[36,37]

The so-called respiratory fluoroquinolones (levofloxacin and moxifloxacin) have good activity in vitro against *S pneumoniae* and practically all the most important respiratory bacterial pathogens. However, in recent years we have seen an increase in pneumococcal strains with reduced susceptibility to fluoroquinolones as a result of the overuse of this antibiotic, with wide geographical variation from one country to another. In Europe, the percentage of pneumococcal strains with reduced susceptibility to fluoroquinolones, as measured by in vitro resistance to ciprofloxacin, a marker of fluoroquinolone resistance, varies from 0.0% in Holland, a country with an excellent antibiotic policy, to 7.1% in Italy, and 10% in Portugal (the European Union country where fluoroquinolones are most prescribed in outpatients).[38,39] The published figures for Spain vary considerably, ranging from 3.2% of strains with reduced susceptibility to levofloxacin in some areas of the country[39] to as high as 9% in others.[40] Although the literature includes some contradictory data on the emergence of pneumococcal resistance to fluorquinolones,[41] it is worth noting that in a recent case series published in Italy 15.1% of the clinical isolates had reduced susceptibility to ciprofloxacin and 5.6% to levofloxacin.[42] The most worrying aspect of this development is that only 3 years earlier (2001) there were no levofloxacin-resistant strains in these areas of Italy. Unlike the pneumococcal strains resistant to β-lactam and macrolide antibiotics, which have their main reservoir in the nasopharynx of children, fluoroquinolone-resistant strains are found primarily in older or recently-hospitalized patients, individuals previously treated with fluoroquinolones, and (interestingly) patients with COPD[43-46]; they also appear to be associated with macrolide resistance.[46]

Another development that should be taken into account is that treatment failure has been reported with levofloxacin in cases of pneumonia caused by resistant pneumococcal strains, some of which acquired resistance during therapy.[47] This happens because the main mechanism of resistance (mutation of the target topoisomerase enzymes that define the helical structure of the bacterial DNA) is a stepwise process: once a single mutation has occurred (which leads to reduced susceptibility to the antibiotic), during or after a second course of treatment the mutation of the second target enzyme occurs relatively easily, resulting in complete resistance that gives rise to treatment failures,[45,47-50] which probably already exceed 20% of cases.[36] 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.[51-54] 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 quinolones) the quinolones played the most important role in the generation of resistance within 3 months of their use.[36] 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.[55] Moxifloxacin, in contrast, displays the highest intrinsic potency against *S pneumoniae*, and this greatly reduces the risk of it inducing resistance to fluoroquinolones.[56] Respiratory fluoroquinolones 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 fluoroquinolones 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.[57]

To minimize the possibility of treatment failure due to resistance acquired during a recent course of treatment, some authors advocate rotation of specific antibiotic regimens in each patient.[36]

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.[5] 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) target resistant gram-positive bacilli, particularly MRSA, while others are more adapted to community-acquired respiratory infections treated in an outpatient (telithromycin, cefditoren)

or hospital (ertapenem) setting. By contrast, between 3 and 7 times more drugs are being approved for the treatment of inflammatory, neoplastic, and endocrinologic processes. Another revealing fact is that no new antibiotics with activity against *Pseudomonas aeruginosa* are scheduled to come onto the market in the next 5 to 10 years despite the fact that we are increasingly obliged to deal with this pathogen due, among other reasons, to the increase in survival among patients with chronic obstructive pulmonary disease (COPD) and severe bronchiectasis.

One exception to this trend is tigecycline, a novel antibiotic of the tetracycline family that was approved by the European Medicines Agency in 2006 for use in hospitals to treat infections of the abdominal organs, skin, and soft tissues. It has a broad spectrum of activity against gram-positive bacteria (including MRSA and enterococci), gram-negative bacteria (including extended-spectrum β-lactamase-producing enteric bacilli), and anaerobes, although it is not effective against *P aeruginosa* or many strains of the *Proteus* species.[58] Of particular note among the drugs at an advanced stage of development are another antibiotic for hospital use called doripenem, a carbapenem very similar to meropenem,[59] and 3 glycopeptides—dalbavancin, oritavancin, and telavancin—which, like vancomycin, mainly target drug-resistant gram-positive bacteria such as MRSA, and to a lesser extent multiresistant *S pneumoniae*.[59-62] There are 2 new fluoroquinolones in an advanced stage of development: sitafloxacin, which, like some other drugs, will not be available in Spain because it causes phototoxicity in Caucasians; and the more promising garenoxacin.[59] It is true that in some countries, for example Japan, a number of antibiotics are used (especially carbapenem β-lactams such as faropenem, panipenem, and biapenem) that display good activity in vitro against pneumococcus and even against strains highly resistant to penicillin. It is possible that these agents may in the future become commercially available in Europe and the USA, as occurred recently with the oral cephalosporin cefditoren, an antibiotic that had been available in Japan for almost a decade.

Because of 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. Finally, high dosage formulas with more favorable pharmacodynamic parameters are coming onto the market and we are more clearly identifying the most active antibiotics, which facilitate more rapid bacterial eradication and minimize the selective pressure for the generation of resistant strains. This is accompanied by a corresponding progressive reduction in the use of the antibiotics likely to induce resistance, such as the macrolides and first- and second-generation cephalosporins. Moreover, there has fortunately been a steady shift towards more energetic short course antibiotic treatment of lower respiratory system infections. While the optimum duration of antibiotic therapy for CAP, nosocomial pneumonia, and COPD exacerbations is not yet known, a growing body of information is available
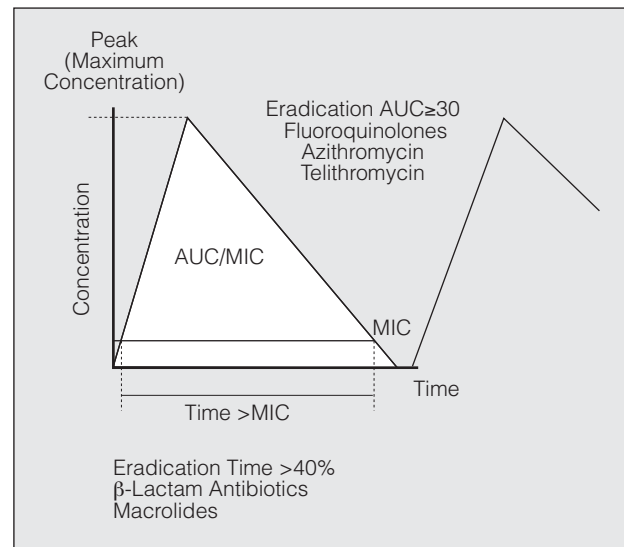

Figure 1. Pharmacodynamic parameters predict bacterial eradication. The presence of low concentrations of antibiotic also induces resistance. AUC indicates area under the concentration-time curve; and MIC, minimum inhibitory concentration.

showing that equally good results can be obtained with fewer days of antibiotic treatment than those traditionally prescribed if appropriate drugs and doses are used. In this respect, serial measurement of procalcitonin, a serum marker of infection, has recently been shown to be effective, not only as an indication of the need for antibiotics, but also as a guide to the optimum duration of treatment in CAP.[63]

We must use the means available to best advantage and to this end we must carry out an in-depth review of the available treatments with a view to ensuring the use of the most active drugs from each group, achieving the best results with these agents, and minimizing the selection of antimicrobial resistance. One of the key aspects of this review will inevitably be a study of the pharmacokinetic and pharmacodynamic profiles of each drug.

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.[64] 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 failure to completely eradicate bacteria contributes to the selective pressure for resistance. The resistant clones that survive at the site of infection and in the nasopharynx of carriers will recolonize 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.[40] Antibiotic activity against a specific bacteria has traditionally been assessed in vitro by measurement of the minimum inhibitory concentration (MIC) using the MIC 90 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.[16,64]

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 for a minimum of 40%-60% of the dosing interval,[13,55,68] although in critical cases it is advisable to aim for even higher concentrations. In practice, it is advisable, whenever possible, to administer the drugs by continuous infusion or at least to administer each dose by slow infusion (2-3 hours), to minimize dosing intervals, and preferably to use a β-lactam antibiotic with a long half-life.[68] 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.[16,64] 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, unadvisable to use ciprofloxacin to treat infections presumed to be pneumococcal.[55] 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*.[68] 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.[36]

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.[40,64]

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[70-100] particularly in 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.[101-105]

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[106] (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,[70] 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 al[107] 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 (erythromycin, roxithromycin, clarithromycin, azithromycin) in the treatment of chronic respiratory diseases. Various studies have shown these drugs to have a variety of beneficial effects in these diseases.[83,108-126] These include an anti-inflammatory effect due to their action on inflammatory mediators (neutrophils, cytokines, nitric oxide), reduced bronchial hyperreactivity, improvement in the rheologic properties of mucous and, more recently, reduction in mucous hyperproduction achieved by reducing mucin synthesis.[127] Other interesting effects have also been described, such as the inhibition of motility, virulence factors, and biofilm formation by *P aeruginosa*.[128,129] Mucoid strains of *P aeruginosa* enclose the bacteria in a biofilm and adhere to mucosal surfaces of the airway; this enhances the organism's resistance to the host's phagocytic activity, increases sputum viscosity, and obstructs antibiotic penetration, thereby facilitating persistence of the pathogen in the airway, that is, colonization. Researchers have identified a regulatory protein that controls the conversion of susceptible strains of *P aeruginosa* to biofilm-producing antibiotic-resistant forms.[130] Manipulation of the components of this protein may play an important role in future treatments. For the first time, in a recent study using in vivo and in vitro analyses, researchers studying the bronchoalveolar lavage of patients with cystic fibrosis found a nontypeable *H influenzae* that forms biofilms in the lower airway.[131]

An interesting study has shown that induction of interleukin-8 expression by airway epithelial cells through interaction with *H influenzae* during both the colonization and exacerbation phases is inhibited by exposure to erythromycin or azithromycin.[132] It is also known that 14- and 15-carbon atom macrolides can facilitate ciprofloxacin penetration into the bacterial biofilm and the elimination of the bacteria within the film.[133] These macrolides have been shown to be clinically useful in diseases such as diffuse panbronchiolitis,[123,134] cystic fibrosis,[108,110,111,114-117,135,136] and bronchiectasis.[108,119,137-145]

Conclusions

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,[146,147] 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 antibiotics are consumed, 80% of which are prescribed to treat respiratory infections.[16] 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,[148] 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.[149] We should commit ourselves to the fight against the self-perpetuating cycle of antibiotic
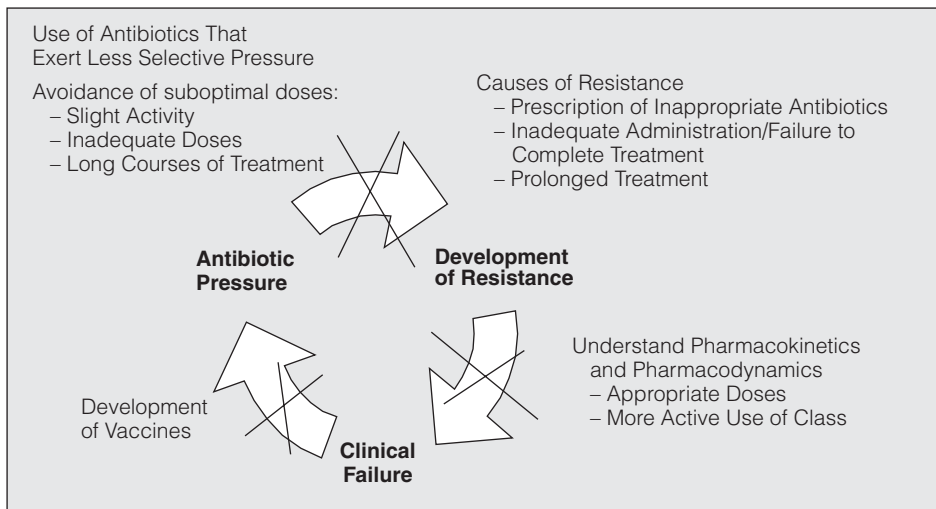
Figure 2. Mechanisms to minimize the self-perpetuating cycle of antibiotic resistance.

pressure creating resistance that leads to clinical failure and eventually even greater antibiotic pressure (Figure 2). The future is in our hands.

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