Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem

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***Abstract*:** Antimicrobial resistance is a global public health challenge, which has accelerated by the overuse of antibiotics worldwide. Increased antimicrobial resistance is the cause of severe infections, complications, longer hospital stays and increased mortality. Overprescribing of antibiotics is associated with an increased risk of adverse effects, more frequent re-attendance and increased medicalization of self-limiting conditions. Antibiotic overprescribing is a particular problem in primary care, where viruses cause most infections. About 90% of all antibiotic prescriptions are issued by general practitioners, and respiratory tract infections are the leading reason for prescribing. Multifaceted interventions to reduce overuse of antibiotics have been found to be effective and better than single initiatives. Interventions should encompass the enforcement of the policy of prohibiting the over-the-counter sale of antibiotics, the use of antimicrobial stewardship programmes, the active participation of clinicians in audits, the utilization of valid rapid point-of-care tests, the promotion of delayed antibiotic prescribing strategies, the enhancement of communication skills with patients with the aid of information brochures and the performance of more pragmatic studies in primary care with outcomes that are of clinicians' interest, such as complications and clinical outcomes.

Keywords: Antibiotic resistance, primary care, point-of-care tests, rational use of antibiotics, strategies

Introduction

Antimicrobial resistance (AMR) is recognized as one of the greatest threats to human health worldwide. Just one organism, methicillin-resistant *Staphylococcus aureus* (MRSA), kills more Americans every year than emphysema, HIV/AIDS, Parkinson's disease and homicide combined [Infectious Diseases Society of America *et al.* 2011]. Globally, 3.7% of new cases and 20% of previously treated cases of tuberculosis are estimated to be caused by strains that are resistant to isoniazid and rifampicin. For decades, these antituberculosis agents have been effective against tuberculosis, but today the effect is insufficient. Nowadays, only one-half of multidrug-resistant tuberculosis is effectively treated with the existing drugs [World Health Organization, 2014]. Extensively drug-resistant tuberculosis (defined as multidrug-resistant tuberculosis plus resistance to any fluoroquinolone and any second-line injectable drug) has been identified in 84 countries globally [World Health Organization, 2013]. Carbapenem-resistant Enterobacteriaceae spp. and extended-spectrum beta-lactamase-producing Enterobacteriaceae have been isolated in recent years [Nordmann *et al.* 2009; Ho *et al.* 2010; Oteo *et al.* 2010; Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, and Pediatric Infectious Diseases Society, 2012]. There is a striking lack of development of new drugs active against these multidrug-resistant Gram-negative bacteria, particularly those producing carbapenemases [Boucher *et al.* 2013], and none of the antibiotics currently available are now effective [Falagas *et al.* 2008; Chen *et al.* 2009; Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, and Pediatric Infectious Diseases Society, 2012].

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While antibiotic resistance has predominantly been a clinical problem in hospital settings, recent data show resistant organisms have also been detected in patients in primary care [National Collaborating Centre for Infectious Diseases, 2010]. A recent report from the World Health Organization (WHO) clearly states that this is not a phenomenon occurring in just poor or developing countries; the problem of AMR is now found throughout the world [World Health Organization, 2014]. Diseases associated with AMR in primary care include tuberculosis, gonorrhoea (specifically *Neisseria gonorrhoeae*), typhoid fever and Group B streptococcus [Centers for Disease Control and Prevention, 2012]. Community-acquired AMR is of particular concern, as these infections can be common and easily transmitted. The most recent data from the European Antibiotic Surveillance Reports found that antibiotic resistance rates of *Escherichia coli* and/or *Klebsiella pneumoniae* vary markedly between countries. Rates of resistant *E. coli* varied 18-fold between Sweden (1.0%) and Greece (18.2%) and for *K. pneumoniae* the differences were even more pronounced, ranging from 0.7% in Sweden to 64.1% in Greece [European Centre for Disease Prevention and Control, 2011]. However, antibiotic resistance of *E. coli* and *Klebsiella* spp. is highest in Asia (≥60%), with rates of 10–30% in Southern Europe, and 5–10% in Northern Europe, Australasia and North America [Livermore, 2012]. European data from 2011 demonstrate an alarming increase in the resistance of these organisms, with around a third of European countries showing a rise in combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides over the previous 4 years [European Centre for Disease Prevention and Control, 2011]. Some of these types of antibiotics are considered by the WHO as 'critically important antimicrobials' in medicine [World Health Organization, 2009], and these broad-spectrum antibiotics should be avoided when narrow-spectrum antibiotics remain effective, as they also increase the risk of *Clostridium difficile* infection, MRSA and resistant urinary tract infections [Public Health England, 2013]. The problem of resistance not only involves the community, it also affects the individual. A recent review describing patients with bacterial urinary tract and respiratory tract infections treated with antibiotics reported that individual resistance may persist for up to 12 months post-treatment, thereby creating situations with the need of requiring second-line antibiotics [Costelloe *et al.* 2010].

Infection with antibiotic-resistant bacteria may cause severe illness, increased mortality rates, and an increased risk of complications and admission to hospital [Kollef, 2008; Paul *et al.* 2010; Livermore, 2012]. According to the European Centre for Disease Prevention and Control, 25,000 people in Europe die each year as a direct result of resistant infection [European Centre for Disease Prevention and Control, 2011]. Antibiotic resistance leads to an increased amount of healthcare costs. It is estimated that complications associated with antibiotic resistance cost €9 billion annually in Europe [Oxford and Kozlov, 2013]. A recent review demonstrated that the additional cost of resistance could be of £20,000 per patient episode in hospital [Smith and Coast, 2013].

In the context of few innovative or new antibiotics in the drug development pipeline, the WHO describes a future of a post-antibiotic world and warns that not only will this eliminate the advances in healthcare made over the past 100 years, which have ensured longer life in most parts of the developed and developing worlds, but it may also result in simple infections becoming unmanageable and potentially fatal [World Health Organization, 2012a, 2012b]. The United Kingdom Chief Medical Officer has highlighted the need for clinicians to preserve the effectiveness of antibiotics by giving clear evidence-based guidance on their appropriate use [Department of Health, 2012] and has stated that we are losing the battle against infectious diseases, and antibiotics may no longer be effective in the long term [Davies *et al.* 2013].

Most of the antibiotics used in medicine are prescribed by general practitioners (GP). In fact, primary care accounts for 80–90% of all antibiotic prescriptions in Europe and most antibiotics are prescribed for respiratory tract infections [European Centre for Disease Prevention and Control, 2014]. Utilization of antibiotics is also very important in other sectors; for instance, approximately 80% of antibiotics in the United States are consumed in agriculture, farming and aquaculture [Hollis and Ahmed, 2013]. Data show a direct correlation between the use of antibiotics and resistance. Countries with a higher consumption of antibiotics show higher rates of resistance [Goossens et al. 2005; Riedel *et al.* 2007]. Antibiotic prescribing differs profoundly from one European country to the next, although

Box 1. Risks that have been shown to be associated with overuse of antibiotics.

Increase of antimicrobial resistance
Increase of more severe diseases
Increase of the length of disease
Increase of the risk of complications
Increase of the mortality rate
Increase of healthcare costs
Increase of the risk of adverse effects, some being life-threatening
Increase of re-attendance due to infectious diseases
Increased medicalization of self-limiting infectious conditions

there is no evidence of differences in the prevalence of infectious diseases. On average, the European consumption rate of antibiotics is 18.3 defined as daily doses/1000 inhabitants/day (DID) in 2010, with the highest rate in Greece with 39.4 DID and the lowest in two Baltic countries with 11.1 DID or 11.2 DID of Holland [European Centre for Disease Prevention and Control, 2010]. A recent study has shown that the consumption of antibiotics is even greater in the new southern and eastern European countries, with an antibiotic use of 42.3 DID in Turkey [Versporten *et al.* 2014].

Apart from spreading resistance, antibiotic overprescribing is also associated with other problems (Box 1). Consumption of antibiotics puts patients at risk of adverse effects. Antibiotics account for approximately 20% of all drug-related emergency department visits in the United States. Although nearly 80% of these visits are attributable to allergic reactions, certain commonly prescribed antibiotics contribute to conditions that range from gastrointestinal to neurologic and psychiatric disorders [Lode, 2010]. Most of these adverse effects are mild, but some life-threatening adverse effects have been reported, such as hepatotoxicity due to amoxicillin and clavulanate [Chang and Schiano, 2007]. Antibiotic overprescribing has been shown to increase patient re-attendance as it medicalizes conditions, which are self-limiting [Little *et al.* 1997]. And more attendance means more prescription of antibiotics.

Why are there such differences in antibiotic consumption in Europe? These differences cannot be explained by a different pattern of infectious diseases across countries. It is clear that the main concern is to avoid under-treatment [Kumar *et al.* 2003]. None of us wants to be seen to have withheld treatment from a patient who subsequently deteriorates, especially if the patient is hospitalized. Although rare, it might damage doctor–patient relationships and lead to complaints and medical–legal consequences. However, most of the respiratory tract infections attended by GPs are self-limiting. In Europe, upper respiratory tract infections account for 57% of the antibiotics used, with a further 30% for lower respiratory tract infections; in contrast, the next most common condition is urinary tract infections at 7% [van der Velden *et al.* 2013]. Moreover, respiratory tract infections are the most commonly treated acute problem in primary care [Francis *et al.* 2009], with most caused by a virus, to which antibiotics have shown to have a limited effect on symptoms. In a recent controlled clinical trial with placebo, with data from the GRACE project (http://www.grace-lrti.org) in 12 European countries including more than 3000 adults with acute cough (≤28 days) and without suspicion of pneumonia based on clinical grounds, the percentage of patients with new or worsening symptoms was slightly less frequently observed among those treated with amoxicillin 3 g daily compared with controls (16% *versus* 19%, number needed to treat = 30) but the prevalence of nausea, diarrhoea, or rash occurred more frequently in the former (number needed to harm = 23) [Little *et al.* 2013a].

The benefits of antibiotic therapy for most respiratory tract infections are modest in the best-case scenario [Kenealy and Arroll, 2013; Spinks *et al.* 2013; Venekamp *et al.* 2013; Smith *et al.* 2014]. If respiratory tract infections are mostly self-limiting, why do we treat between 52% and 100% of the cases, with a median of 88%, with antibiotics? [Ashworth *et al.* 2005]. As mentioned recently by Hay and Tilling, how is it possible that

88% of patients with acute bronchitis are special [Hay and Tilling, 2014]?

In general, prescribing has been shown to be influenced by several factors, including cultural aspects related to the country background, socio-cultural and socio-economic factors, and the cultural beliefs of the patient and the prescriber, patient demand, and clinical autonomy [Butler *et al.* 1998; Moore and McNulty, 2012]. In different countries, people hold different ideas about health, causes of disease, labelling of illness, coping strategies, and treatment modalities [Hulscher *et al.* 2010]. Diagnostic uncertainty plays an important role in antibiotic overprescribing [Harbart and Samore, 2005]. In a Dutch study, the use of antibiotics was strongly associated with uncertainty avoidance (unwillingness to accept uncertainty and risks). The authors also observed that hierarchical societies such as those in Southern Europe consume more antibiotics than mainly egalitarian societies such as Scandinavian countries, the UK or the Netherlands [Deschepper and Vander Stichele, 2001]. Socioeconomic factors have also been associated with variability of antibiotic prescription. Aspects such as the way in which healthcare is funded or reimbursed, the percentage of generic drugs in the market, the economic incentives or the pressure of pharmaceutical industries can affect antibiotic prescription by clinicians [Hulscher *et al.* 2010]. Inequalities might also explain the variability of antimicrobial use. Moreover, Kirby and Herbert observed a moderate correlation between AMR and income inequality with the utilization of data from 15 large European countries [Kirby and Herbert, 2013].

Other factors related to the professional care-delivery system of antibiotics are probably important, such as care coordination, professional's collaboration, communication teamwork, clinician's knowledge about management of infectious diseases and doctor–patient relationship. Misconceptions and uncertainties regarding the role of antibiotics also exist among patients [Altiner *et al.* 2007]. For example, a European study reported that around half of the patients believed antibiotics were effective in treating viruses, cold and flu, with considerable differences across countries [European Commission, 2010]. There also appears to be a dissonance between physician and patient expectations during a consultation of a respiratory tract infection [Coenen *et al.* 2013]. Clinicians' attitudes on antibiotics also play an important role in antibiotic overprescribing. A recent survey including more than 1000 GPs carried out in the UK found that 55% felt under pressure, mainly from patients, to prescribe antibiotics, even if they were not sure that they were necessary, and 44% admitted that they had prescribed antibiotics to get a patient to leave the surgery [Cole, 2014].

Prescribing fewer antibiotics is needed

A reduction in antibiotic consumption leads to a reduction of resistance. The classical Finnish study focusing on macrolide resistant *Streptococcus pyogenes* clearly showed how a reduction in macrolide use could lead to a reduction in AMR. Antibiotic resistance dropped from 9.2% in 1997 to 7.4% in 2000, with a statistically significant association between regional macrolide resistance and consumption rates [Bergman *et al.* 2004].

What can we do to prescribe fewer antibiotics? Our goal is not just to reduce the amount of antibiotics. It is also to promote a rational use of antibiotics by prescribing antibiotics only to patients who are expected to benefit from the treatment. Many studies have been performed to determine the effectiveness of different types of intervention in promoting a more rational use of antibiotics. According to the last Cochrane review on interventions to improve antibiotic prescribing, multifaceted interventions combining physician, patient and public education in a variety of venues and formats were the most successful. Interactive educational meetings were more effective than didactic lectures, but levels of improvement were limited. Inappropriate antibiotic prescribing was reduced by less than 20% across a broad range of study populations [Arnold and Straus, 2005; Gonzales *et al.* 2013]. In a recently published paper, van der Velden and colleagues assessed the effectiveness of physician-targeted interventions aiming to improve antibiotic prescribing for respiratory tract infections in primary care. The authors included 58 studies and found that overall antibiotic prescribing was reduced by 11.6%. Within the 59 interventions aiming to decrease overall antibiotic prescribing, it was found that concurrently performed interventions (multiple interventions) were more effective than single interventions focusing on only one issue. Multifaceted interventions that included educational materials for physicians were the most effective strategies. The authors observed that communication skills in training and near-patient testing achieved the largest intervention effects [van der Velden *et al.* 2012]. The Cochrane review showed that interventions aimed at reducing overall antibiotic prescribing were less effective than interventions focusing on adherence to first choice antibiotics [Arnold and Straus, 2005]. However, other reviews have reported the opposite [van der Velden *et al.* 2012]. In general, multifaceted interventions were associated with an average increased prescribing of first-choice antibiotics of approximately 10% [Steinman *et al.* 2006]. The strategies for primary care that have been observed to be most successful are presented in this review.

Enforcement of governmental laws prohibiting over-the-counter sale of antibiotics

Self-medication with antibiotics is common in many parts of the world. In several countries, antibiotics are sold, illegally, without a prescription [Morgan *et al.* 2011]. This is particularly common in many countries in Asia, Africa, South and Central America, and even in Southern European countries, such as Italy, Spain, Greece and Malta [Borg and Sciclunca, 2002; Väänänen *et al.* 2006; Carrasco-Garrido *et al.* 2008; Plachouras *et al.* 2010]. In some countries, antibiotics are also available on the free market, i.e. outside pharmacies. Law enforcement to prohibit the illegal over-the-counter sale of antibiotics at pharmacies and the sale of antibiotics for humans and animals on the free market should be promoted worldwide.

Antimicrobial stewardship programmes, campaigns and audits

In many countries, there have been educational campaigns that aim to change healthcare professional and patient behaviour in antibiotic consumption. Interventions include the publication of guidelines, educational sessions on appropriate prescribing of antibiotics, educational sessions on the diagnosis and management of infectious diseases, review of prescribing data for practices, local interviews by pharmacists, messages included on TV, radio and other mass media, etc. Although the effects of these public campaigns and primary-care projects are positive, they are not sufficient to reduce the problem of AMR. An analysis of 22 national- or regional-level campaigns in high-income countries from 1990 to 2007 did find a reduction in antibiotic use. However, as all but one campaign targeted the patient and healthcare professional simultaneously [Huttner *et al.* 2010], it cannot be concluded whether patient education and awareness alone is an effective intervention to decrease antibiotic use. However, some campaigns have been particularly successful. Interventions targeting doctors and patients in primary care with the active participation of GPs in audits with discussion of results obtained have been found to be effective in achieving a reduction of antibiotics prescribed, as was found in the European-funded project Happy Audit [Bjerrum *et al.* 2011]. The Scottish Antimicrobial Prescribing Group, established by the Scottish Government in 2008, led a national initiative to actively address antimicrobial stewardship with the development of prescribing indicators for hospital and primary care, and observed reductions in antibiotic prescribing with no adverse effect on mortality or AMR patterns [Nathwani *et al.* 2012]. In Sweden, the Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA) and Surveillance of Resistance antimicrobial stewardship initiative reported a reduction in antibiotic use and lowered AMR rates over 10 years, without measurable negative consequences [Mölstad *et al.* 2008].

More evidence from pragmatic studies carried out in primary care is required

GPs often state that the patients attended are special and they need antibiotics; in fact, clinicians think their use is associated with a more rapid recovery or because they have an underlying comorbid condition, such as asthma, chronic lung disease, or they are smokers or have purulent sputum, and because of these features they need antibiotics. These are the so-called 'special situations', and many GPs claim that published clinical trials published usually do not take these patients into account. However, in recent years some good-quality papers have been published considering these special situations, including patients with outcomes that are of interest to GPs, such as clinical outcomes with length of symptoms and incidence of complications [McNulty *et al.* 2013]. The publication of these pragmatic studies can help GPs believe the results obtained. One example is the recent study on the low number of complications found in patients with sore throat (quinsy, otitis media, sinusitis, impetigo or cellulitis), observed in 1.3% of the cases, regardless of whether they were treated with antibiotics [Little *et al.* 2013b].

Promoting the use of valid point-of-care tests

If you visit a primary-care consultation in a Scandinavian country and compare it with a similar consultation in a Southern European country, you soon realize that the most important difference is the number of diagnostic tools available in Scandinavia. GPs in Northern countries usually use rapid antigen detection testing for the diagnosis of streptococcal pharyngitis, C-reactive protein (CRP) devices for ruling out serious respiratory tract infections, equipment capable of determining the number and type of leukocytes and agar plates for urine culture and susceptibility testing of bacteria (e.g. Flexicult plates, Petri plates that give clinicians knowledge about the bacterial aetiology of a urinary tract infection and the susceptibility pattern of the involved microorganisms in less than 24 hours).

The major contribution of point-of-care tests seems to decrease doctors' uncertainty, adding useful information that helps to identify who to treat or not to treat with antibiotics. However, not all of the rapid tests are useful in primary care; only those that are accurate, precise, easy to use and interpret, fast and affordable for a primary care setting are acceptable [Cals and van Weert, 2013]; but above all, point-of-care tests should be able to predict prognosis and expected response to antibiotic treatment. In primary care, as opposed to the hospital, knowledge about the aetiological agent of an infection is not the most important thing; it is more important to be able to predict the expected evolution of the infectious disease and thereby consider the potential effect of an antibiotic treatment [Llor and Butler, 2014]. Several point-of-care tests have been shown to be effective in reducing the number of antibiotics prescribed. For example, CRP rapid testing, which gives the result in less than 3 minutes, has been shown to significantly reduce antibiotic prescribing in lower respiratory tract infections without compromising the clinical evolution of the patients [Huang *et al.* 2013]. In a recent trial, carried out in six European countries, Internet-based training on the CRP rapid test was associated with a significant reduction of antibiotics prescribed for acute lower respiratory tract infections [Little *et al.* 2013c]. Two Dutch studies showed significant decreases in antibiotic prescriptions when GPs used CRP testing to guide antibiotic management in lower respiratory tract infections, observing reductions from 53% to 31% in one study [Cals *et al.* 2009] and from 56.6% *versus* 43.4% in the other [Cals *et al.* 2010]. Furthermore, no differences in clinical outcomes were observed between patients treated and not treated with antibiotics.

Distinguishing pneumonia from acute bronchitis with only clinical findings is problematic in primary care, and the use of CRP rapid testing has been shown to perform better in predicting the diagnosis of pneumonia than any individual or combination of clinical symptoms and signs in lower respiratory tract infection [Hopstaken *et al.* 2003; Flanders *et al.* 2004; van Vugt *et al.* 2013]. The addition of the CRP level together with the signs and symptoms of a lower respiratory tract infection predicts the diagnosis of pneumonia better [van Vugt *et al.* 2013]. CRP tests have also proven to be a good predictor of clinical evolution in acute exacerbations of mild-to-moderate chronic obstructive pulmonary disease, being much better than the classic Anthonisen criteria (purulence of sputum, increased coughing or increase of dyspnoea) [Llor *et al.* 2012]. CRP has also been useful for achieving a reduction of antibiotics prescribed for acute sinusitis [Bjerrum *et al.* 2004]. The use of procalcitonin has been shown to be effective in reducing the amount of antibiotics in patients with lower respiratory tract infections [Tang *et al.* 2009]. However, it takes approximately 20 minutes to perform the test.

The utilization of rapid antigen-detection tests or Strep A has been associated with a lower prescribing of antibiotics for patients with sore throat. McIsaac and colleagues reported a 45% reduction in antibiotic prescribing in adults using rapid tests compared with empirical treatment [McIsaac *et al.* 2004]. Worrall and colleagues reported a proportion of antibiotic prescribing of 58% among physicians who did not use these rapid tests and 27% among those who did use this rapid test [Worrall *et al.* 2007]. Similarly, in another primary-care study carried out in Switzerland, the use of Strep A reduced antibiotic prescribing from 60% to 37% [Humair *et al.* 2006]. Curiously, in recent studies carried out in paediatrics, in which the incidence of streptococcal infection is higher, greater reductions were observed, with percentages of antibiotic prescription ranging from 22% to 28% among physicians assigned to rapid testing [Maltezou *et al.* 2008; Ayanruoh *et al.* 2009]. However, despite the fact that the use of these rapid antigen detections tests reduces the percentage of antibiotics prescribed, some recent papers cast doubts on the clinical benefit of their use. In a retrospective analysis of 726 patients, post-streptococcal complications were observed in a substantial number of patients with negative results, thereby limiting the usefulness of this rapid point-of-care test [Dingle *et al.* 2014]. We clearly need new rapid diagnostic instruments that allow clinicians to make a rapid decision on the basis of their results [Laxminarayan *et al.* 2013].

Promoting delayed prescribing of antibiotics

Delayed antibiotic prescribing means that the prescriber delivers an antibiotic prescription, but recommends the patient not to redeem it the same day. The prescription should only be redeemed if the patient feels worse within a few days. If symptoms reduce spontaneously, the prescription should be discarded. Delayed antibiotic prescribing is a widespread practice in the UK and its use is enforced by national guidelines [National Institute for Health and Clinical Excellence, 2008], but it has been difficult to implement in other countries. However, recent evidence from Norway also indicates that delayed prescribing may lead to a reduction in antibiotic use, mainly for sinusitis and otitis media [Høye *et al.* 2013].

A Cochrane review evaluated outcomes of delayed antibiotic prescribing compared with immediate antibiotic or no antibiotic prescribing in patients with respiratory tract infections. The study found that delayed prescribing was not superior to no prescribing in terms of symptom control, such as fever and cough, and complications [Spurling *et al.* 2011]. However, in a recently published study, researchers from Southampton showed a significant reduction in the consumption of antibiotics among patients assigned to delayed antibiotic strategies (less than 40%), without prejudice to the patients' outcome, compared with the strategy of immediate antibiotic therapy [Little *et al.* 2014a]. Moreover, the authors pointed out that giving these patients responsibility for their own treatment apparently helps them to consult less frequently in the future. This is a likely and interesting explanation. They concluded that discussing concerns and expectations of patients and informing them of the natural course of an uncomplicated lower respiratory tract infection might reduce reconsultation rates. This has particularly been studied in acute pharyngitis, in which the group of patients assigned to delayed prescribing presented a lower incidence of complications when compared to the group in which antibiotic therapy was withheld and was associated with a lesser re-attendance in subsequent episodes compared with immediate prescribing [Little *et al.* 2014b].

Enhancing communication skills with patients

Improved communication in primary care can help to bridge this gap between physician and patient expectations. This can be achieved using various approaches. In a pragmatic clinical trial carried out in the Netherlands the authors observed that GPs assigned to CRP testing prescribed fewer antibiotics than those in the control group (30.7% *versus* 35.7%) and those trained in communication skills treated 26.3% of all episodes of respiratory tract infection with antibiotics compared with 39.1% treated by family physicians without [Cals *et al.* 2013]. The STAR programme of five sessions of Web-based training in enhanced communication skills, with patient scenarios and an expert-led face-to-face seminar, achieved a 4.2% reduction in global antibiotic use with no significant changes in admissions to hospital, reconsultations or costs [Butler *et al.* 2012]. Francis and colleagues showed that the use of a brief Web-based training programme and an interactive booklet on respiratory tract infections in children with uncomplicated respiratory tract infections within primary-care consultations led to an important reduction in antibiotic prescribing, with an odds ratio of 0.29 and reduced intention to consult without reducing satisfaction with care [Francis *et al.* 2009]. Gonzales and colleagues conducted a three-group randomized study at 33 primary-care practices in the United States in acute bronchitis patients, evaluating the effectiveness of two interventions: in one-third of the practices, the intervention was printed decision support in which educational brochures were given by triage nurses to patients with cough as part of routine care, and in another third of the practices a computer-assisted decision support intervention was implemented so that when triage nurses entered 'cough' into the electronic health record, an alert would prompt the nurse to provide an educational brochure to the patient; the remaining practices were control sites. Compared with the baseline period, the percentage of subjects prescribed antibiotics for uncomplicated acute bronchitis during the intervention period decreased from 80% to 68.3% at the printed decision support intervention sites and from 74% to 60.7% at the computer-assisted decision support intervention sites [Gonzales *et al.* 2013].

Communicating the possible length of mainly bothersome complaints, such as cough, is important in acute bronchitis, since the mean duration of any cough is between 15 and 20 days. In a recent study, Ebell and colleagues performed a population-based survey in the United States to determine patients' expectations regarding the duration of acute cough, reporting a median duration of 5–7 days [Ebell *et al.* 2013]. The mismatch between patients' expectations and reality for the natural history of acute cough illness has

Box 2. Communication tips that can help with patients with self-limiting respiratory tract infections.

Discuss with the patient that antibiotics do not significantly reduce the duration of symptoms of self-limiting respiratory tract infections and that they may cause adverse effects and lead to antibiotic resistance.

Back up the information provided with a leaflet or brochure given to the patient highlighting the most important information.

Set realistic expectations for symptom duration, including the average total duration of symptoms (after seeing the doctor): 4 days for acute otitis media, 1 week for acute sore throat, 1½ weeks for common cold, 2½ weeks for acute rhinosinusitis and 3 weeks for acute cough/bronchitis.

Define the diagnosis as a viral respiratory infection, chest cold, or sore throat instead of using the medical terms 'acute bronchitis' and 'acute tonsillitis'.

Clearly explain the red-flag symptoms patients should know about infectious diseases.

Consider delayed prescription of antibiotics in those situations in which an aetiology cannot be clearly established.

Consider the use of rapid tests in cases of doubt, such as C-reactive protein rapid testing or rapid antigen detection tests, and discuss the results with the patient.

important implications for antibiotic prescribing. If a patient expects that an episode will last about 1 week, it makes sense that they might seek care for that episode and request an antibiotic after 5 or 6 days. Notwithstanding, GPs often fail to satisfactorily communicate the mean length of cough to patients with acute bronchitis [Cals *et al*. 2007]. As physicians, we must avoid sentences such as: 'With these pills you will feel a rapid remission of your cough;' and, as the cough will not remit the patient will be prone to reconsult again and will probably demand medicine that is perceived as stronger, such as antibiotics. Educating patients about the natural history of infectious diseases is therefore crucial. Patients need to know that antibiotics are probably not going to be beneficial in most self-limiting infections, and that treatment with antibiotics is associated with significant risks and side effects. They should also be told that it is normal to still be coughing 2 or even 3 weeks after onset, and that they should only seek care if they are worsening or if an alarm symptom, such as high fever, bloody or rusty-coloured sputum, or shortness of breath occurs (Box 2). Careful word selection for the infection is also important [Phillips and Hickner, 2005]. One survey showed that patients were less dissatisfied after not receiving antibiotics for a chest cold or 'viral upper respiratory infection' than they were for acute bronchitis [Phillips and Hickner, 2005].

The use of information brochures is of aid. In the last few years, many studies on the benefit of discussing the evolution of the infectious conditions with the patient have been published. It is important to talk about the expected duration of symptoms and to deliver written material that explains when the patient should contact again in case of a possible deterioration (Box 2). Some papers have shown that a patient's awareness of the red-flag signs reassures and helps to better comply with the treatment regimen and the use of fewer antibiotics [Butler *et al*. 2012]. In a recent clinical trial in which the effect of an online course on improving communication skills along with the use of leaflets was evaluated, the group of GPs assigned to this intervention prescribed 32% fewer antibiotics compared with the control group, and those who were trained in this strategy and at the same time had access to CRP rapid testing in their consultations, reduced antibiotic prescribing by 62% [Little *et al*. 2013a]. In addition, patients assigned to this strategy better understood why they had to take antibiotics. Communicative aspects have to contemplate what patients are unaware of, such as side effects of antimicrobial agents or their lack of effectiveness in infections that are self-limiting, even in many of these 'special situations' [Moore *et al*. 2014]. Box 2 describes some aspects that GPs should consider when communicating with patients with self-limiting respiratory tract infections.

Conclusion

There is no reason to explain why antibiotic prescribing in respiratory tract infections (the most frequent primary care) is so great. Doctors have to do well and not harm, while respecting the ethical principles of autonomy and justice. However, in the case of ethical conflict, nonmaleficence and justice (at a public and obligatory level) take precedence. We know that we can reduce antibiotic prescribing in many of the infections that are currently unnecessarily treated without compromising our patients' health. By accomplishing this, we will do less harm. Moreover, we know that antibiotics can stop being effective in the short and medium term. The use of the strategies discussed in this paper will help GPs to reduce prescribing of antibiotics. Our duty is to prescribe antibiotics only when they are necessary, i.e. in less than 20% of the infectious seen in primary care.

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