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"Ten commandments" for the appropriate use of antibiotics by the practicing physician in an outpatient setting

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A multi-national working group on antibiotic stewardship, from the International Society of Chemotherapy, put together ten recommendations to physicians prescribing antibiotics to outpatients. These recommendations are: (1) use antibiotics only when needed; teach the patient how to manage symptoms of non-bacterial infections; (2) select the adequate ATB; precise targeting is better than shotgun therapy; (3) consider pharmacokinetics and pharmacodynamics when selecting an ATB; use the shortest ATB course that has proven clinical efficacy; (4) encourage patients' compliance; (5) use antibiotic combinations only in specific situations; (6) avoid low quality and sub-standard drugs; prevent prescription changes at the drugstore; (7) discourage self-prescription; (8) follow only evidence-based guidelines; beware those sponsored by drug companies; (9) rely (rationally) upon the clinical microbiology lab; and (10) prescribe ATB empirically – but intelligently; know local susceptibility trends, and also surveillance limitations.

Keywords: antibiotic stewardship, antibiotic resistance, guidelines, generic antibiotics, self-prescription, treatment compliance

INTRODUCTION

Appropriate use of antimicrobials is defined by the WHO as "the cost–effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance" (WHO Department of Communicable Disease Surveillance and Response, 2001). Antimicrobial resistance is one of the most urgent health threats people are facing all around the world.

The Antimicrobial Stewardship Working Group of the International Society of Chemotherapy was established in 2009, with the aim of promoting a judicious use of antimicrobials by fostering collaboration on a global scale. Nowadays, the five continents are

represented in our group, and experts from all of them have participated in the creation and discussion of these 10 tips and top action items for the practicing physician in an outpatient setting. These recommendations aim to guide physicians who prescribe antibiotics (ATB) to do so with caution, in order to maintain the usefulness of these pivotal therapeutic tools.

The members of the working group understand that there are many other factors that strongly cause the misuse of ATB, such as their use in agroindustry and veterinary practice (at least half of the worldwide production), the deficient medical education regarding antimicrobial stewardship, the poor or non-existent control of ATB production, marketing, and promotion, the lack of community-oriented information on ATB use, and a weak regulation of drugstores that triggers self-prescription, among others. However, we are convinced that if the following simple action items are widely known and applied, it would greatly contribute to improve antimicrobial usage. The present document summarizes our recommendations to improve the use of ATB in outpatient settings.

USE ANTIBIOTICS ONLY WHEN NEEDED; TEACH THE PATIENT HOW TO MANAGE SYMPTOMS OF NON-BACTERIAL INFECTIONS

Studies worldwide show that at least half of prescribed ATB are not necessary or otherwise abused (Gonzales et al., 2001; Akkerman et al., 2004; Castro et al., 2008; Dryden et al., 2009). Therefore, despite the obvious nature of this recommendation, physicians need to embrace this notion. For instance, ATB are often prescribed against viral infections: 50–80% of patients displaying viral symptoms receive ATB (Linder and Stafford, 2001; Castro et al., 2008; NIHCE, 2008; Vergison et al., 2010). A particular case is pharyngitis, where at least 80% of the cases have a viral etiology (Cooper et al., 2001; Bisno et al., 2002), and there are clear criteria to assess when and how to treat (Centor et al., 2007). The very need for using ATB against streptococcal pharyngitis in countries where rheumatic fever is not a problem, is controversial (Del Mar et al., 2006; NIHCE, 2008). Otitis media (in children without high fever or vomiting) (Little et al., 2001a,b; Spurling et al., 2007) is another example where ATB are abused; the patient (or the patient's parents) would benefit from a brief explanation of supportive measures (anti-pyretics, baths, hydration, etc.), the neglectable outcome difference with or without ATB, and the very common adverse reactions, such as diarrhea or rash, that might outweigh the benefit of using ATB in upper respiratory tract infections (Linder, 2008; Coker et al., 2010). Spending a few minutes educating our patients so that they understand the impact of antibiotic abuse, might prevent them to seek a colleague willing to prescribe ATB. Other situations where ATB may not be needed include: (a) fever without other signs and symptoms of infection; (b) self-limiting bacterial infections, such as many diarrheal diseases (Chiu et al., 1999; Sirinavin and Garner, 2000); (c) asymptomatic bacteriuria, except during pregnancy (Tambyah and Maki, 2000; Nicolle et al., 2005); and (d) asymptomatic colonization of skin ulcers, sores, and wounds. The role of ATB in the management of exacerbations of chronic bronchitis (Puhan et al., 2007), fever and minor infections in immunosuppressed patients, and atypical community-acquired pneumonia (CAP) in outpatients (Mills et al., 2005; Shefet et al., 2005), is also controversial. A review of ATB use and abuse has been recently published (Leekha et al., 2011).

SELECT THE ADEQUATE ATB; PRECISE TARGETING IS BETTER THAN SHOTGUN THERAPY

This should be another obvious recommendation, but prescriptions of aminoglycosides for CAP or ceftriaxone for urinary tract infections (UTI), for instance, are so common, that this is clearly an issue. Physicians must know the prevalent pathogens for each kind of infection, and the local susceptibility trends (also, ideally, the local prevalence of resistance mechanisms). Despite the many different bacteria that cause infections in humans, in the outpatient setting there is only a handful of relevant organisms: *Streptococcus pneumoniae*, *S. pyogenes*, and *Haemophilus influenzae* causes most bacterial respiratory infections; uropathogenic *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae* causes most UTI; enteropathogenic *E. coli*, *Salmonella* spp., and *Shigella* spp. causes most enteral infections; *Staphylococcus aureus* and *S. pyogenes* causes skin and soft-tissue infections; *Neisseria gonorrhoeae* is the most relevant sexually transmitted pathogen; *H. influenzae* and *N. meningitidis* causes bacterial meningitis. Susceptibility trends of these pathogens (see recommendation number 10) should be available in a local, timely fashion, so that they can guide empirical therapy.

Narrow spectrum drugs should be preferred when possible: wide-spectrum is only necessary when potential causative pathogens are very diverse, or when the infection is potentially polymicrobial. Wide-spectrum aminoglycosides are a bad choice against pneumococcal infections (hence, not adequate for nearly half lower respiratory tract infections), and third-generation cephalosporins are excessive for most cases of otitis media or UTI (in fact, plain amoxicillin is usually enough, instead of "using a cannon to shoot a fly"). Once a drug class has been selected, it is important to avoid using those more likely to select for resistance, such as long-half-life macrolides (Baquero, 1999), or low-potency fluoroquinolones (Credito et al., 2010).

CONSIDER PHARMACOKINETICS AND PHARMACODYNAMICS WHEN SELECTING AN ATB; USE THE SHORTEST ATB COURSE THAT HAS PROVEN CLINICAL EFFICACY

Most dosage indications for ATB are decades old, when data on PK, PD, and resistance was still emerging. In some cases, changes have been made, such as the evolution of aminoglycoside dosing, from three times per day to only once; but many deficiencies are still hidden in standard treatment schemes. Physicians must review available data on PK/PD in order to adequately select drugs and dosing, and to prevent resistance (Li and Tang, 2005; Craig and Slauch, 2009; Mazzei et al., 2009; Leekha et al., 2011). Drugs belonging to the same family may significantly differ, so that they are not exchangeable.

Starting in the early 1980s, ATB can be classified as concentration- or time-dependent; aminoglycosides, fluoroquinolones, colistin and metronidazole are concentration-dependent, while beta-lactams and most macrolides are time-dependent (Craig, 2001). This classification is useful in designing

rational dosing schemes, but this information often arrived after prescribing information was written. Also, ATB are almost always used in adults in fixed doses, unlike the common adjustments made by pediatricians. It is unlikely that a patient of 1.50 m and 45 kg would need the same dose as another of 1.90 m and 110 kg; perhaps ATB dosing must now be adjusted for weight (Falagas and Karageorgopoulos, 2010), to avoid prescribing too little or too much of a drug. The global increase in human weight has forced to recalculate the average weight of passengers in airplanes and ships, but this recalculation is still missing in drug dosing.

The length of ATB treatments was also developed when the main concern was efficacy and safety – but not resistance. Hence, treatments were unnecessarily long. There are not enough clinical trials designed to measure the efficacy of shorter courses, but well-done studies have demonstrated it for UTI (Arredondo-García et al., 2004; Vogel et al., 2004; Kyriakidou et al., 2008; Lutters and Vogt-Ferrier, 2008), acute otitis media (Kozyrskyj et al., 2010), acute exacerbations of chronic bronchitis (El Moussaoui et al., 2008; Falagas et al., 2008), acute streptococcal pharyngitis (Altamimi et al., 2009), and acute sinusitis (Falagas et al., 2009). In contrast, there is no supporting evidence for many of the traditional 10–14 day ATB courses, which are based more on conventional wisdom or expert opinion (Mouton et al., 2011). Although there are many factors to be considered (infection site, involved pathogen, tissue concentration and PD of ATB, etc.) short courses have comparable efficacy with less exposure, less side effects, less risk of resistance development and less cost. In brief: shorter is better (Harbarth et al., 2000; D'Agata et al., 2007; Mouton et al., 2011). Therefore, whenever available, physicians must rely on published information, and shorten treatments if possible; physicians' resistance to shorten treatments will only foster bacterial resistance to ATB.

ENCOURAGE PATIENTS' COMPLIANCE

The best ATB would fail if the patient does not comply with the treatment. Compliance (i.e., taking the indicated doses at the indicated time periods, and completing treatment as prescribed) is in average only around 50%; there are many strategies that the physician can use to improve patients' compliance (Buxton, 2006). Communication is key in this regard: physicians must ensure that the patient understood the prescription, assist him/her in scheduling doses according to their activities, suggest when possible the use of devices, from pill casings for hours or days, to the use of PDAs or cell phones with programmable alarms. Drugs that require only one or two doses per day usually have better compliance rates; injectable ATB, on the other side, are associated to premature discontinuation of treatments (and, with the exception of benzylpenicillin, are often completely unnecessary in the outpatient setting). Lack of compliance can potentially lead to resistance, due to repeated exposure to sub-inhibitory concentrations of ATB, that foster the emergence of resistance (Cebrián et al., 2006; Henderson-Begg et al., 2006; Linares et al., 2006; Cortes et al., 2008). Patients' understanding of this risk, as well as its health and economic consequences to him/her, and to his/her relatives is a responsibility that physicians must take the moment they prescribe an ATB.

USE ANTIBIOTIC COMBINATIONS ONLY IN SPECIFIC SITUATIONS

Combinations of antibiotics increase the exposure of bacteria to these drugs, which select resistance, increase the costs and have more chance of being accompanied by side effects resulting from drug interactions. For community-acquired infections, the best drug for the job is usually a single one. Notable exceptions include, of course, the management of tuberculosis, where combining drugs is the best way to prevent resistance; the therapy of moderate to severe CAP of unknown etiology, that may include pneumococci (usually susceptible to beta-lactams, but growingly resistant to macrolides) or "atypical" bacteria (intrinsically resistant to beta-lactams, but susceptible to macrolides) can be treated with combinations of beta-lactams and macrolides before resorting to fluoroquinolones (Miyashita et al., 2006; Mandell et al., 2007; Menéndez et al., 2010). Management of *Helicobacter pylori* infections also require ATB combinations. The emerging threat of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) causing skin infections, can often be faced by adding sulfamethoxazole–trimethoprim or clindamycin, to the beta-lactam usually prescribed for this kind of diseases (Ruhe et al., 2007; Levy Hara et al., 2009). However, combinations lacking supporting evidence, that many physicians use "just in case," should be avoided.

AVOID LOW QUALITY AND SUB-STANDARD DRUGS; PREVENT PRESCRIPTION CHANGES AT THE DRUGSTORE

Terms "low quality" and "sub-standard" are used here to refer to generic drugs that do not meet the requirements of bioequivalence (98–102% of active ingredient as labeled, 85–125% of maximum plasma concentration, C_{max}, and time-concentration area under the curve, AUC, of the original drug). Unfortunately, even those minimal requirements are not considered by national health authorities of many countries. Bioequivalence is not necessarily a test for clinical efficacy (Vesga et al., 2010); furthermore, lack of quality control, corruption, counterfeit drugs, deficient control at drugstores, etc. (Newton et al., 2010), common in developing countries, diminish the confidence on generic drugs. Additionally, even in developed countries, generic drugs are sub-standard (Del Tacca et al., 2009). Low quality ATB may result in pharmacokinetic profiles much different from the ones of original drugs which, in turn, may create increased periods of time of sub-inhibitory concentration exposure, leading to treatment failure and/or resistance. This is not, of course, a problem plaguing all generic drugs; many products have shown to be bioequivalent to original ones (Mazur et al., 1999; Galan-Herrera et al., 2009). But the "burden of evidence" should rely on generic manufacturers, which should demonstrate clinical efficacy instead of only bioequivalence. In many countries it is also a common practice from drugstore salespeople to change physicians' prescriptions. Physicians must alert patients of this practice, which is also a risk for a complete change of drug or modified-release formulation. (The working group that developed these recommendations is aware that this one is controversial and, in many developing countries, unaffordable; however, we urge the reader to consider it, within the local market and financial features).

DISCOURAGE SELF-PRESCRIPTION

Self-prescription, or otherwise non-medical prescription (which includes the advice of relatives, friends or drugstore salespeople) is not the main cause of antibiotic abuse in most countries, and is not corrected only by requiring prescriptions to buy antibiotics. However, the use of ATB in these uncontrolled and often unnecessary conditions is high in developing countries, ranging from 20 to 40% (Drug Utilization Research Group, 1997; Amábile-Cuevas et al., 1998; Gaur and English, 2006; Grigoryan et al., 2010). From the physician's point of view, communication with patients is again pivotal to prevent self-prescription: discussing, in lay terms, the consequences of antibiotic abuse and its impact on their health and economy, must go along with ATB prescription. Promoting compliance (see recommendation number 4) also reduces a common source of self-prescription: the use of ATB leftovers, often inadequate and expired. If communication with local pharmacists is possible, physicians must stress the societal risk that ATB self-prescription poses, so that this practice is minimized.

FOLLOW ONLY EVIDENCE-BASED GUIDELINES; BEWARE THOSE SPONSORED BY DRUG COMPANIES

Therapeutic guidelines have recently become the basis of therapeutic choices. Realizing this trend, pharmaceutical companies often sponsor all sorts of guidelines and recommendations, pushing for the inclusion of newer, more expensive treatment options, but lacking experimental evidence of their superiority upon older and cheaper drugs. Some medical journals also join this trend by allowing such biased recommendations to be published, commonly as supplements (Rochon et al., 1994). It is crucial to look for guidelines based on systematic reviews of available literature, describing levels of evidence, instead of those merely stating "expert opinions" (Hippocrates once said: "There are in fact two things, science and opinion; the former begets knowledge, the latter ignorance"). It is unfortunately common to find guidelines developed by specialists' societies or groups, recommending the use of more expensive ATB in the absence of evidence of superiority over cheaper options; the levels of evidence to sustain such recommendations are often not consistent with the literature.

Aside, it can also be argued that even the best treatment guidelines are only focused on efficacy and safety, but miss the societal side of ATB, i.e., the resistance promotion side. Furthermore, some mathematical models predict that the use of guidelines encourage the intensive use of just some drugs, which rapidly select for resistance (Laxminarayan and Weitzman, 2003). It is important to encourage the inclusion of resistance analyses in therapeutic guidelines, aside of efficacy and safety concerns. Finally, if medicine were purely a matter of guidelines, an appropriate software may easily replace the physician; guidelines universalize individual problems, and make us face them with a very limited range of options.

RELY (RATIONALLY) UPON THE CLINICAL MICROBIOLOGY LAB

The microbiology laboratory can provide significant support in some cases of infection, although in most cases it is only used when a first ATB empirically prescribed has failed. By performing cultures for the diagnosis of prevalent infections (UTI, diarrhea) the patient can be treated in an adequate and safe way. However, the lab cannot provide reliable answers in some cases, such as lower respiratory tract infections, where the etiology can be assessed in no more than half of the cases. On the other hand, the lab input is unnecessary, as when trying to know the etiology of pharyngitis (or the susceptibility of *S. pyogenes* to beta-lactams). Physicians must be familiar with the laboratory their patients are referred to: it should have well-documented quality controls, reference strains, etc., so that it provide reliable results. This is particularly necessary in countries where clinical labs run without major supervision from health authorities. It is also crucial to know how to collect a useful sample, and what are the limitations of each analysis (e.g., a nasal swab is not adequate for assessing the etiology of sinusitis; and standard susceptibility testing cannot consider many pharmacokinetic and PD factors that affect clinical efficacy). By choosing a good lab, and using it only when the information it would provide is really meaningful, patients will save money and antibiotic prescription will improve.

PRESCRIBE ATB EMPIRICALLY –BUT INTELLIGENTLY; KNOW LOCAL SUSCEPTIBILITY TRENDS, AND ALSO SURVEILLANCE LIMITATIONS

The need for surveillance of resistance has been highlighted many times (German et al., 2001; WHO Department of Communicable Disease Surveillance and Response, 2001; O'Brien and Stelling, 2007), but there are limited efforts to monitor resistance globally. Developing countries often lack reliable surveillance programs, especially of community-acquired pathogens (Tenover et al., 2001; Chaitram et al., 2003); data in developed countries is of better quality (Bronzwaer et al., 2002), and can even be linked to usage patterns. However, the amount of susceptibility data is overwhelming: local and international meetings of infectious diseases societies are full of posters and symposia on it. Many of these data are generated by projects sponsored by pharmaceutical companies, hence it is important to read them carefully. Simple contradictions may reveal bias or plain wrongdoing: if two fluoroquinolones perform significantly different against *E. coli* isolates, or if the prevalence of MRSA is very different from the resistance prevalence toward amoxicillin–clavulanate, or if a set of pneumococci are highly resistant to fluoroquinolones but very sensitive to macrolides, we must suspect the quality and/or transparency of these results. Furthermore, many susceptibility surveillance projects are inherently biased; researchers rely on isolates from clinical labs, but physicians only send patients to the lab when facing complications or initial failure of empirically prescribed drugs. Resistance prevalence data may therefore be overestimated (Lopardo et al., 2007), precluding the use of ATB that might actually work.

FINAL CONSIDERATIONS

Tips that can be singled out: avoid ATB for bronchitis when pneumonia is not a concern; avoid ATB for watery diarrhea when dysentery of typhoid fever is not a concern; delay the use of ATB against otitis media for at least 48 h; consider nitrofurantoin instead of fluoroquinolones against uncomplicated cystitis; reserve respiratory fluoroquinolones for unresponsive or high-risk CAP patients; and avoid fixed-dose combinations of ATB and anti-inflammatory or anti-histaminic drugs.

Preventing bacterial diseases is a much better way to avoid the use of ATB and all of its consequences. Vaccines reduce disease prevalence and ATB demand. Immunizations against influenza, pneumococci, *H. influenzae* B, meningococci, and *Salmonella* Typhi can have a pivotal role in reducing the need for ATB.

Pharmaceutical companies provide us with great drugs and continuously invest in research and development; but the marketing side is only aimed at promoting the use of their products including, of course, ATB. Through many strategies, pharmaceutical companies strongly influences prescribing behaviors, in ways not necessarily supported by the best evidence; papers sponsored by *big pharma* are often biased (Chren and Landefeld, 1994; Rochon et al., 1994; Levy Hara et al., 2006; Anderson et al., 2009). Of course, this does not only affects ATB prescription, but due again to the societal nature of ATB effects, the trend, as well as the lack of adequate regulation in many countries, makes it particularly dangerous in terms of public health. Physicians must keep this in mind.

ATB are limited, non-renewable resources (Carlet et al., 2011), that we all need during our lives. "Every antibiotic expected by a patient, every unnecessary prescription written by a doctor, every uncompleted course of antibiotics, and every inappropriate or unnecessary use in animals or agriculture is potentially signing a death warrant for a future patient" (Dryden et al., 2009). We should not wait for governments to implement measures that regulate drug promotion and usage, and enforce ethical codes. Change must start with us all.

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