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Outpatient Antibiotic Prescription in the South of Portugal

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ABSTRACT

Background: Antibiotic abuse and misuse are recognized as important determinants for bacterial antibiotic resistance. Although there are frequent calls to stop the unnecessary use of antibiotics, both consumption and resistance are escalating over the world.

Objective: To assess the antibiotic prescription and its determinants in the Algarve, for different infectious diseases in Primary Care.

Method: A Drug Use Study (Prescription-Indication Study) was performed in a convenience sample of 70 general practitioners (GPs) working in the Algarve (Portugal). During the study period each GP consecutively selected 20 patients with an antibiotic prescription for systemic use, characterizing their clinical and therapeutic profiles.

Results: About 81% (57/70) of the invited GPs returned the requested data. A total of 925 patients were included in the study, 40% of them male. Patients' mean age was 41.4 years (range: 1 to 94; SD=24.14). Respiratory (50.5%) and urinary tract infections (29.8%) were the infectious conditions more frequently treated, accounting for 80.3% of the total. Penicillins were the antibiotics most prescribed (43.7%), followed by macrolides (20.15%) and quinolones (19.3%), the last two preferably prescribed by older GPs. For respiratory infections, younger GPs prescribed penicillins more frequently (62.1%) than other GPs. While treating the same infections, female GPs prescribed significantly more macrolides (40.5%) than males (29.6%).

Conclusion: Considering the costs, side effects and growth of bacterial resistance, it is important to improve antibiotic prescribing as much as possible. Developing effective interventions to reduce inappropriate antibiotic prescribing will require a clear understanding of the predictors that influence the prescribing behaviour.

INTRODUCTION

The emergence of multiresistant microorganisms, both in humans and in animals, suggests the imperative need for intervention on the pattern of use of antibiotics, considering that this is a major determinant in the selection and dissemination of these microorganisms [1]. Although there are frequent calls to stop the unnecessary use of antibiotics, both consumption and resistance are escalating all over the world [2].

It is estimated that 80-90% of antibiotic prescriptions for systemic use occurs in Primary Care [3-5]. Moreover, it is believed that about 50% of prescribed antibiotics in Primary Care are not actually required [6-8], since many of the infections treated with antibiotics have a viral aetiology [9-11]. Uncertainty in diagnosis is one of the main reasons leading to over-prescription and prescription of broad-spectrum antibiotics [12-14], mainly due to difficulty in distinguishing between viral from bacterial infections, thus hindering proper treatment [14,15].

Among the various monitoring strategies for the use of medications, we highlight the studies on medical prescription. Prescribers play an important role in promoting the rational use of medicines. Therefore, the analysis of their prescribing habits provides a better understanding of some aspects related to the quality of therapeutics, allowing the identification of problems, implementation of corrective and educational actions, and assessment the impact of these measures [16].

The relationship between prescribing patterns and the characteristics of physicians is complex. To Cadieux et al [17] some factors have emerged to explain the differences in antibiotic prescribing among physicians:

- Lack of physician knowledge.
- Pharmaceutical detailing.
- Physician training environment, possibly through professional tradition, cultural expectations or pharmaceutical detailing.
- Practice experience (time in practice).
- Increased antibiotic prescribing over time may also be due to physician "softening" to patient demand for antibiotics.
- Increased practice overload and lack of time to facilitate patients understanding and find mutual and beneficial therapeutic decisions.

In spite of a decrease in the consumption of antibiotics in recent years, Portugal still features high numbers when assessing consumption in defined daily dose per 1000 inhabitants. In order to study the antibiotic use pattern and its determinants in the Algarve (Portugal), we performed an epidemiological study aiming to characterize antibiotic prescription for different infectious diseases in Primary Care.

METHODS

Study design

A Drug Use Study (Prescription-Indication Study) with a crossover design was performed in a sample of General Practitioners (GPs) from a universe of 280 physicians practicing in public health centres in the Southern region of Portugal (Algarve). At least one physician was conveniently selected in each of the 16 participating health centres.

Selection of study subjects: During a 2 months period, each participant GP consecutively selected 20 patients who had an antibiotic prescription for systemic use and collected information through the methodology proposed by Caldeira et al [18].

Measurements

The data collection comprised therapeutic, clinical and socio-demographic profiling through a questionnaire to be completed by the physicians involved from November 2010 to January 2011. Demographic and professional characteristics of the GPs were also collected.

Outcomes and statistical analysis: The dependent variable for this study was the type of antibiotic prescribed which were classified according to the ATC Classification System. Three variables for ATC classification codes corresponding to the 3rd, 4th and 5th levels were also defined.

The independent variables were related to the prescriber: gender, age, degree of medical career, years of clinical practice and prescription local (urban/rural). Independent variables were also related to the Indication of the antibiotic. The conditions for which antibiotics were indicated were classified according to the classification ICPC-2 (*International Classification of Primary Care* - 2nd ed).

Statistics were performed using SPSS v17 statistical software. A preliminary analysis used descriptive statistics for the quantitative variables (central tendency and dispersion measures), while absolute frequencies and percentages were obtained for the qualitative variables. Bivariate analyses were performed using Chi-square and Fisher exact tests for categorical variables. The level of significance was set at 0.05 with a confidence interval of 95%.

Ethical approval

This study was approved by the Ethics Committee of the Regional Health Administration of the Algarve (Ref. 327/10 DEP, 16/6/2010).

RESULTS

Physicians' data

From the 70 General Practice and Family Medicine physicians selected, 57 returned at least one antibiotic prescription

record, corresponding to 81%. Twenty-six of the participating physicians were male (48.1%) and 28 were female (51.9%). Regarding age, 14 (26.4%) were between 30 and 44 years old, 17 (32.1%) between 45 and 54 and 22 (41.5%) 55 or older. Ages ranged from 30 (minimum) to 65 (maximum). We found that 55.8% of physicians had 25 or more years of clinical practice, with an average of 23.9 ± 9.9 years. On the other hand, 45.3% had a category of graduate assistant and only 13.2% were head of department. The vast majority practice in places with urban characteristics, 60.4% in predominantly urban areas and 26.4% among mmoderately urban areas.

Patients' data

A total of 925 patients were included in the study, 40% of them male. Patients' mean age was 41.4 years (range: 1 to 94; SD=24.14), with 63.3% under 40 years old. A total of 943 medicines were prescribed for systemic use (1.02 per patient on average) for different infectious conditions. Respiratory (50.5%) and urinary tract infections (29.8%) were the conditions more frequently treated, accounting for 80.3% of the total.

Table 1 presents the distribution of the prescribed antibiotics by ATC level 4. Penicillins (J01 CA, J01CE, J01F e J01CR) were the antibiotic group most prescribed (43.6%), followed by macrolides (20.1%) and quinolones (19.3%). Amoxicillin-clavulanic acid (21.3%), amoxicillin (13.9%), ciprofloxacin (13.5%), azitromicin (10.0%) and clarithromycin (8.7%) were the antibiotic molecules (ATC level 5) more frequently prescribed. Amoxicillin was present in about 81% of the prescriptions of penicillins (J01CA04 and J01CR02). It is noteworthy the low prescription of Beta-lactamase sensitive penicillins (J01CE). Also cephalosporins account for 8.4% of total antibiotics prescribed. This emphasizes the fact that third-generation cephalosporins (J01DD) represent 26.6% of all prescribed cephalosporins, and were more often prescribed than first-generation cephalosporins.

Table 1. Prescription of the major groups of antibiotics-ATC4 level.

ATC4	Frequency	Percentage
Tetracyclines - J01AA	12	1.3
Penicillins with extended spectrum – J01CA	133	14.1
Beta- lactamse sensitive penicillins - J01CE	26	2.8
Beta-lactamase resistant penicillins - J01CF	51	5.4
Combinations of penicillins, inc. beta-lactamases inhibitors - J01CR	201	21.3
First-generation cephalosporins - J01DB	19	2.0
Second-generation cephalosporins -J01DC	39	4.1
Third-generation cephalosporins - J01DD	21	2.2
Combination of sulfonamides and trimethoprim - J01EE	24	2.6
Macrolides -J01FA	183	19.4
Lincosamides -J01FF	7	0.7
Other aminoglycosides - J01GB	2	0.2
Fluoroquinolones – J01MA	182	19.3
J01XC – steroids antibacterials	8	0.9
Imidazole derivatives – J01XD	3	0.3
Nitrofuran derivatives – J01XE	8	0.9
Other antibacterials – J01XX	24	2.6
Total	943	100.0

Table 2 presents the prescription of the main groups of antibiotics (penicillins, cephalosporins, macrolides and quinolones) in ATC3 level according to the conditions by tract or affected organ. Penicillins (49.0%) and macrolides (35.1%) were more frequently prescribed for respiratory infections, while quinolones (51.0%), penicillins (16.1%) were the most common for urinary infections. Remarkably, about 90% of prescriptions for macrolides occurred in respiratory infections and more than 50% of quinolones have been used for urinary tract infections. Cephalosporins have been used with some frequency in various infections. The differences found for the prescription of these groups of antibiotics according to the different infections have statistical significance (χ^2=337.630, p<0.001).

Table 2. Prescription of the major groups of antibiotics (ATC3 level) according the pathologies.

Grupo ATC3	Pathologies						Total N (%)
	Respiratory N (%)	Urological N (%)	Skin N (%)	Digestive N (%)	Ear N (%)	Other Diagnoses N (%)	
Penicillins J01C	228 (57.3)	30 (7.5)	52 (13.1)	37 (9.3)	46 (11.6)	5 (1.3)	398 (100)
Cephalosporins J01D	34 (43.6)	10 (12.8)	13 (16.7)	4 (5.1)	15 (19.2)	2 (2.6)	78 (100)
Macrolides J01F	161 (89.4)	1 (0.6)	3 (1.7)	6 (3.3)	5 (2.8)	4 (2.2)	180 (100)
Quinolones J01M	36 (20.5)	96 (54.5)	25 (14.2)	7 (4.0)	7 (4.0)	5 (2.8)	176 (100)

In respiratory infections, younger GPs prescribed penicillins more frequently (62.1%) than other doctors, while older GPs prescribed more macrolides (38.7%) and quinolones (12.4%) **(Table 3).** These associations were statistically significant (χ^2=16.109; p=0.013). For the same infections, female GPs prescribed more macrolides (40.5%) than male (29.6%), while male

GPs prescribed more cephalosporins, more penicillins, and more quinolones than female practitioners. These associations were also statistically significant (χ^2=9.729; p=0.021). On the other hand, we found that physicians with less years of clinical practice prescribed penicillins more frequently, while physicians with 25 or more years of practice prescribed cephalosporins, macrolides and quinolones more frequently. However, the differences were not statistically significant (χ^2=4.804, p=0.569).

Table 3. Prescription of ATC3 groups in the tract respiratory infections according the characteristics of the physician.

	Penicillin J01C	Cephalosporin J01D	Macrolides J01F	Quinolones J01M	Total
Age (Years)					
30-44	64 (62.1)	8 (7.8)	27 (26.2)	4 (3.9)	103 (100)
45-54	57 (45.6)	13 (10.4)	46 (36.8)	9 (7.2)	125 (100)
≥ 55	79 (42.5)	12 (6.5) χ^2=16.109	72 (38.7) p=0.013	23 (12.4)	186 (100)
Gender					
Masculino	102 (49.5)	22 (10.7)	61(29.6)	21 (10.2)	206 (100)
Feminino	106 (47.7)	11(5.0) χ^2= 9.729	90 (40.5) p=0,021	15 (6.8)	222 (100)
Years of clinical practice					
<10	28 (62.2)	3 (6.7)	12 (26.7)	2 (4.4)	45 (100)
10-24	58 (50.9)	8 (7.0)	38 (33.3)	10 (8.8)	114 (100)
≥ 25	114 (45.6)	20 (8.0) χ^2= 4.804	92 (36.8) p=0.569	24 (9.6)	250 (100)
Stage in the medical career					
Internal GP/Assistant GP	83 (52.5)	10 (6.3)	50 (31.6)	15 (9.5)	143 (100)
Graduate Assistant/Consultant	85 (41.1)	21 (10.1)	82 (39.6)	19 (9.2)	188 (100)
Head of Department	32 (65.3)	2 (4.1) χ^2=12.595	13(26.5) p=0.050	2 (4.1)	47 (100)
Place of professional practice					
APU	135 (47.9)	22 (7.8)	94 (33.3)	31 (11.0)	282 (100)
AMU	51 (49.0)	9 (8.7)	40 (38.5)	4 (3.8)	104 (100)
APR	22 (52.4)	2 (4.8) χ^2=8.305	17 (40.5) p=0.217	1 (2.4)	42 (100)

APU-Urban area; AMU-Moderately Urban Area; APU-Predominantly Rural Area

The prescription of the main groups of antibiotics in respiratory tract infections was independent of the stage in the medical career (χ^2=12.595, p=0.050). Nevertheless, it was found that physicians who were at the top of the career prescribed penicillins most frequently and less often cephalosporins, macrolides and quinolones for the same infections.

In predominantly rural areas the prescription of penicillins and macrolides was more frequent when compared with the prescription in urban areas. Prescription of quinolones was more frequent in predominantly urban areas and prescribing cephalosporins was more frequent in moderately urban environment. However, the association between prescription of the main groups of antibiotics for respiratory infections and place of prescription had no statistical significance (χ^2=8.305, p=0.217).

DISCUSSION

The results have shown that infections of the respiratory system led to more antibiotic prescriptions (53%), followed by infections of the urinary tract (20%), skin (11%), ear (8%) and digestive (6%) as found in 2001 by Falcão et al [19]. However, the results of prescription studies vary widely, stemming from different methodologies and different populations observed, although respiratory infections are the predominant ones in the various studies analysed.

Many authors have questioned the prescription of antibiotics in clinical situations where a bacterial infection is not likely to happen (e.g. upper respiratory infection and influenza) [20-25]. According to our study, we assume that considering the high frequency of antibiotics prescribed for respiratory infections, it is probable that an unnecessary prescription has also happened. Therefore, specific strategies to help GPs reduce antibiotic prescribing are necessary and could include measures such as writing delayed prescriptions, improving communication skills and disseminating patient information leaflets. Addressing clinical uncertainty is also important if physicians are to have confidence in advising their patients that antibiotics are not needed [26].

Penicillins were the most prescribed group of antibiotics, which is not surprising because this type of antibiotic is the first choice for many infectious diseases in the community. In our study, penicillins in combination with β lactamase inhibitors represented 21.3% of total prescriptions (about 50% of the prescribed penicillins) and broad-spectrum penicillins accounted for 13.9% of this value. The scientific literature often refers the low use of beta lactamases sensitive penicillins (J01 CE), especially because they are given as the first choice in the treatment of acute tonsillitis [27] and this is, in many studies, one of the most frequent indications for the prescription of antibiotics [18,25,28,29]. This is also the case in our study. The preference for the combination of

amoxicillin with clavulanic acid may be related to poor patient acceptance of parenteral administration and, on the other hand, the greater perception of the development of resistance to amoxicillin by the agent commonly involved in the tonsillitis, *S. pyogenes*. However, it is known that a combination with clavulanic acid has no benefit because the resistance mechanism does not result in the production of enzymes, increasing only the potential to cause adverse effects [30]. **Table 4** summarizes the main side effects of the top classes of antibiotics [31].

Table 4. The main side effects of the top classes of antibiotics [31].

Grupo ATC3	Antibiotic Class Members	Main side effects
Penicillins J01C	Penicillin, amoxicillin, amoxicillin-clavulanate, ampicillin, piperacillin-tazobactam, nafcillin, oxacillin	Rash, diarrhea, abdominal pain, nausea/vomiting, drug fever, hypersensitivity (allergic) reactions, acute anaphylactic shock.
Cephalosporins J01D	Cephalexin, cefaclor, cefuroxime, ceftibuten, cefdinir, cefixime, ceftriaxone	Rash, diarrhea, nausea/vomiting (rare), hypersensitivity (allergic) reactions, serum sickness, vaginal candidiasis
Sulfonamides J01E	Trimethoprin-sulfamethoxazole, erythromycin-sulfisoxazole, sulfadiazine	Nausea/vomiting, diarrhea, anorexia, abdominal pain, rash, photosensitivity, headache, dizziness
Macrolides J01F	Erythromycin, azithromycin, clarithromycin	Abdominal pain, diarrhea, anorexia, nausea/ vomiting, rashes, taste alterations (clarithromycin)
Quinolones J01M	Ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin	Nausea/vomiting, diarrhea, abdominal pain, headache, lethargy, insomnia, photosensitivity (can be severe), rashes

Second generation cephalosporins were the most prescribed, in particular cefuroxime. The 3rd generation cephalosporins (J01DD) accounted for 26.8% of the prescribed cephalosporins and were more often prescribed than the 1st generation ones. This situation is likely to be related to the greater number of cases of urinary tract infections when compared with other studies. For example, in our study, urinary infections accounted for 20%, while the study by Falcão et al represented 15% of the cases [19]. Although our study did not quantify specific cystitis, we believe this is the most common infection of the urinary tract. According to various sources [32,33], the antibiotics indicated primarily for the treatment of uncomplicated cystitis are nitrofurantoin, fosfomycin and cotrimoxazole (in regions with resistance <20%). In the present study, ciprofloxacin was the most prescribed antibiotic in infections of the urinary tract. More than 50% of urinary tract infections were treated with quinolone, emphasizing the low use of nitrofurantoin and fosfomycin. In the absence of data on bacterial resistance, physicians participating in this study have chosen a broader therapeutic spectrum. In a study conducted in 2012 in the Algarve region, with the aim of ascertaining the prevalence of infectious agents in urinary infections and their antimicrobial resistance patterns, a high rate of susceptibility to fosfomycin (85%) and nitrofurantoin (81%) was found for *E. coli*. This shows that treatment protocols with such antibiotics are suitable for the Algarve region and therefore it is of interest to streamline the implementation of clinical standards, increasing their acceptance among the medical community [34].

In our study, in the case of respiratory infections, penicillins were prescribed more often by younger physicians, while cephalosporins were more often prescribed by doctors in the 45-54 age group. With regard to macrolides and quinolones, their most frequent prescribers were physicians aged 55 and over. In the same type of infection, male gender was significantly associated with higher prescribing of cephalosporins and female gender with more frequent prescription of macrolides. We could not find any explanation for this association.

The prescription of antibiotics, in respiratory tract infections, was independent of the category in the medical career, even at the limit of statistical significance (p=0.050). The doctors at the top of the career prescribed penicillins most frequently and less frequently cephalosporins, macrolides and quinolones. A comparative analysis of the association between physicians' characteristics and the prescription pattern is not easy considering the diversity of methodologies used and the few studies on this subject. In a systematic review conducted by Lopez-Vazquez et al it was concluded that with the exception of years of clinical practice, physicians' socio-demographic factors do not significantly influence the prescription of antibiotics [35]. However, Zoutman et al concluded that older doctors chose fewer antibiotics of first choice in streptococcal pharyngitis [11]. Caldeira et al found that physicians with 10 or more years of clinical practice prescribed more penicillin (J01C), in particular amoxicillin and clavulanic acid for tonsillitis, bronchitis and pneumonia [18]. For bronchitis, female doctors prescribed penicillins the most, and in turn, male doctors prescribed more cephalosporins. In this sense, the present results follow this previous trend.

This study has several limitations that must be taken into account when interpreting the results. One limitation is related to the data collection method, based on self-reported prescribing. Physicians might be motivated to present their prescribing practices in the best light. The high participation rate in our study may suggest a participation or sampling bias [36,37]. Practitioners with a greater knowledge in the use of antibiotics were those who agreed to participate and/or a greater concern with the issue of bacterial resistance. A snowball sampling approach completed the group of participating physicians. This inclusion method does not ensure the representativeness of the sample and the results achieved cannot, therefore, be generalized.

CONCLUSION

This study was not designed to evaluate the quality of the prescription, but it allowed building evidence that suggests further research and public health intervention in the Algarve. Knowing the low use of antibiotics considered the first choice for tonsillitis and urinary infections and the high level of prescription of quinolones and 3rd generation cephalosporins, at least additional information initiatives are needed for this group of practitioners.

Considering the costs, side effects and growth of bacterial resistance, it is important to improve antibiotic prescribing as much as possible. Developing effective interventions to reduce inappropriate antibiotic prescribing will require a clear understanding of the predictors that influence the prescribing behaviour. This information will be important to improve medical education, medical practice and therefore, public health in the future.

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POTENTIAL CONFLICTS OF INTEREST

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