Social and demographic determinants in the prescription of systemic antibiotics

Aspetti sociali e demografici della prescrizione di antibiotici sistemici

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INTRODUCTION

The introduction of antimicrobials in the 1940 decade represented one of the major medical advances of all times, in spite of which, infectious diseases are still the most frequent reason for consultation in Primary Care, originating more than 90% of the prescription of systemic antibiotics. Spain is one of the developed countries with more consumption of antibiotics and major rates of bacterial resistances, especially in the community pathogens (Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Campylobacter jejuni, Salmonella or Escherichia coli) [1]. The information on antibiotics consumption in Spain is impressive: it was the second European country with major consumption in the year 1997 and in 2000, 20 patients out of 1000 received antibiotic treatments daily [2, 3].

The excessive consumption of antibiotics and the appearance of bacterial resistances against antibiotics are related directly to the medical inadequate prescription, the dispensation without a prescription from the pharmacists and the indiscriminate patients’ use of it. Other related factors are the pharmaceutical campaigns, for the pressure they put on the prescription and the sanitary administration, for the lack of a policy of antibiotics in Primary Care [4]. To improve the consumption of antibiotics we should take steps to correct people’s behaviour and involved institutions and establish policies of rational use of antibiotics in every sanitary area.

MATERIAL AND METHODS

Area of study

Castile and Leon is an interior region located in the centre of the Iberian Peninsula, which has a border with nine Spanish communities and with Portugal. It has a surface of 94,224 km² which is 18.7% of the total national surface, forming the most extensive region of Spain. The climate is continental, characterized by strong contrasts, low rainfall, frosts in winter and high temperatures in summer.

Information on consumption

The information used in the study comes from the statistics of antimicrobial consumption from 2001 to 2005 obtained from the information system of drugstore called “Concyliu” (5). It is a system of analysis and evaluation of the pharmaceutical service, aimed at the areas of Management, Evaluation and Pharmaceutical Inspection that has a database of drugs and sanitary products named “Remedios” that is drawn
from the files of the Ministry of Health and Consumption and of the Spanish Agency of the Medicine, from the files of dietician products and from foreign specialities from other manual load specialities.

On analysing this information of consumption it is necessary to have in consideration a series of facts:

1. The information about Concylia does not include the hospital antibiotics consumption, since every hospital acts as “a great individual”, and acquires it mainly from the manufacturer. But it shows the expense from the prescription when the patient is discharged from hospital, urgency services or external consultation.

2. It does not show the sales of prescriptions in private surgeries, nor the consumption from other managing entities different from the National Health System. We have solved this problem using the database of the sanitary card, which displays better the real assisted population.

3. It does not give information of self-medication consumption, which in some previous studies exceeds up to 12% of the total sales of antibiotics [6, 7].

4. On the other hand, and producing an overestimation of the antibiotics consumption, is the fact that not everything sold is consumed, because there are patients who give up their treatment before finishing them. In some studies that use as source of information the interview, this figure is approximately 42% [8].

5. We do not include in these figures the antibiotics sold in drugstores that are used for the treatment of animals, approximately 8% [9-13] and antibiotics that are used as promoters of animals’ growth, which is a considerable part of the production, more than 40% in total weight [14].

The information obtained was from principle active, and we analyze the whole consumption from the prescription of antibacterial that are included in the classification Anatomical Therapeutical Chemical Classification Index of the group J01: antibiotics of systemic use. There were not included therefore anti-infective drugs different from this group: urinary antiseptic (G04A), antmycotic of systemic use (J02), antimycobacterial (J04), antiviral of systemic use, immunological serum and immunoglobulin (J06) and vaccines (J07). All the evaluated antibiotics were systemic with independence of the route of administration and therefore there were not included prepared dermatological, ophthalmological or otorhinolaryngological topics in whose composition there are antibiotics of this group.

**Description of consumption indicators**

**Number of DDD per 1000 inhabitants and day (DID)**
The defined daily dose (DDD) is a unit of measure to quantify the consumption of drugs recommended by the World Health Organization for the use in the accomplishment of studies of medicines utilization.

By means of the DDD, we relate the qualitative elaborated variable active principle (grouping all the specialities of common composition) to the quantitative elaborated variable Number of DDD per 1000 inhabitants and day [15-17] (DID), which is interpreted as a measure of the prevalence relative to the use, according to the following formula:

\[ \text{DID} = \frac{\text{SU} \times \text{PF}/\text{P} \times Q/\text{PF} \times 1000}{\text{DDD} \times \text{Inhabitants} \times 365 \text{ days}} \]

SU: sold units; PF/P: number of pharmaceutical forms per container; Q/PF: quantity of product in every pharmaceutical form.

Although not exactly, it fits the number of persons in 1000 that receive this pharmacological treatment every day. We can work out sums among different drugs, and the result of this calculation is the prevalence of utilization of the group. This value is the one that we will use to establish increases or decreases from one year to another.

**Processing and analysis of information**

Databases were constructed with the programs Excel and Access for the processing of the information. The analysis of the information was done fitting the model ANOVA (Analysis of the Variance) by means of the procedure GLM (Generalized Linear Model) included in the statistical system SAS (North Caroline).

### RESULTS

**Analysis of the geographical variability of the antibiotics consumption of systemic use**

The global consumption per sanitary area for the whole studied period showed noticeable differences (Figure 1), so that the major antibi-
otics consumption of systemic use was in the area of Avila with 22.37 DID, followed by Zamora (21.83 DID), Salamanca (21.0 DID), Soria (20.67 DID), Palencia (18.97 DID), Leon (17.56 DID), Burgos (16.59 DID), Segovia (16.50 DID), East Valladolid (16.36 DID), The Bierzo (16 DID) and in last place West Valladolid (13.46 DID). It is interesting to point out that the difference between the first one and the last one was almost 9 DID.

On the other hand we analysed the evolution from 2001 to 2005 of the consumption in every sanitary area, and we observed three different patterns (Figure 2): on the one hand the areas of Avila, Burgos, Salamanca and Zamora presented a curve with constant changes through the period though with a final trend towards a more raised consumption in 2005. On the other hand The Bierzo, Leon, Segovia and Soria with the same inflexions showed a smaller final trend in the last two years of the study. Finally both areas of Valladolid and Palencia presented a constant and almost uniform growth of the consumption during the whole period.

To point out possible qualitative differences of consumption we did an analysis of the subgroups and more significant active principles consumed. Figures 3 and 4 show the five most prominent therapeutic subgroups, reflecting the following facts: Avila presented the most important consumption from wide spectrum penicillins (around 6.50 DID) while Burgos showed...
the lower consumption of the same group with 3.35 DID. Penicillins associated to inhibitors of beta lactamase presented a very changeable consumption among different areas, with figures over 6 DID in Zamora, Burgos, Avila and Salamanca, whereas we observed a minimum in both areas of Valladolid around 4 DID. In the macrolides group, Leon was the area with the highest consumption (3.15 DID), followed very closely by Zamora, Salamanca and Soria, being the lowest that of Segovia (1.83 DID). The quinolones had major significance in Salamanca (2.94 DID) and less in Segovia and West Valladolid (1.73 DID); and on the other hand it was in this area where cephalosporins point out a lower relative consumption (near 1 DID). Cephalosporins stood out due to a much raised consumption in Soria and Zamora, trebling the consumption of other areas like Valladolid.

The differences per geographical area were more obvious when we studied the main active principles of antibiotics of systemic use. In Figure 5 we analysed comparatively the consumption of the principal penicillins during the 2001-2005 period, taking into account the following facts: amoxicillin-clavulanate was the active principle most used in the majority of the different areas highlighting Burgos, The Bierzo and Salamanca. In Avila, Palencia, Segovia and East Valladolid the consumption of amoxicillin...
was slightly superior to that of the amoxicillin-clavulanate, though we underline the case of Avila with an important use of the two active principles. Cephalosporins showed much lower consumption data in all the areas, though its use is significant in Soria (cefoxime) and in Leon and Zamora (cefixime). The differences per area were greater in the macrolides subgroup than in the penicillins (Figure 6). The use of clarithromycin was clearly superior in respect with the rest of active

**Figure 5** - Distribution of the consumption of principal penicillins and cephalosporins in DID according to the area.

**Figure 6** - Distribution of the consumption of the main macrolides in DID according to the area.

**Figure 7** - Distribution of the consumption of the main quinolones, tetracyclines and sulfamides in DID according to the area.
principles in all the areas except in The Bierzo, though with diverse figures among areas, presenting a maximum in Zamora (1.67 DID) and a minimum in The Bierzo (0.68 DID). Azithromycin was the most used macrolide in The Bierzo, though other areas showed similar consumptions such as Leon, Salamanca and Soria. A low consumption stood out in Palencia and Segovia.

With regards to the rest of active principles of this subgroup we only underline the consumption of eritromicine and roxitromicine in East Valladolid.

In Figure 7 we represent the rest of active principles of antibiotics of systemic use with an important consumption, stressing the following aspects: ciprofloxacin and norfloxacin were the most prescribed active principles of the quinolones group, being ciprofloxacin the most important in all areas, showing a maximum peak in Salamanca (1.18 DID) and a minimum in West Valladolid (0.65 DID). Moxifloxacin showed a consumption far below with regard to the active principles commented above, showing a stable use, and it was in a range of 0.2-0.4 DID.

As for tetracyclines, doxicicline presented a similar consumption in all areas standing out for its high prescription Segovia and Avila, remaining in the rest below 0.3 DID.

To finish the consumption of sulfamethoxazole-trimethoprim had a stable prescription in all areas, about 0.2 DID.

**DISCUSSION**

**Geographical variability in the antibiotics prescription**

There are diverse circumstances that can influence the differential consumption of antimicrobial among regions. First, the demographic structure is undoubtedly one of the most important factors that take part in the antibiotics consumption in a certain area, so that the children and the elderly are potentially major consumers of this therapeutic group [18]. Secondly, the epidemiology of the infections, being cold zones more predisposed to respiratory infections as it demonstrates the casuistry of the majority of these processes. Finally, according to information given by the doctors in the “Study on the antibiotics use in Spain”, respiratory low infections are more frequent in the rural area (30.4%) than in the urban one (22%), but figures are the opposite regarding ear/paranasal sinus-es infections (16.2% in the urban area and 7.6% in the rural one) [19].

Antibiotics consumption differences between diverse geographical areas are well established in the comparative study of the several studies done in Europe, though they present the problem of contrasting methodologies (sources of information, indicators, assigned population ...) and different times (the variation throughout the years is strongly confirmed), one can deduce important differences in consumption and patterns of antibiotics prescription throughout time, which do not match a geographical or epidemic determined pattern in different countries, autonomous communities and provinces of our country, and even in the same province [2, 3, 20-31]. Therefore, other factors, alongside the prescription habits, determine these differences in the patterns of use in the different geographical zones, throughout the time. In this way, Cars et al. and Goosens et al. allude to medical attitudes, cultural and social factors and differences in the health systems that regulate the medicine utilization [3, 23]. García-Rey et al. analyze climatological conditions, the demographic structure, the educational level, incomes and the number of sanitary resources of the population as determinant factors of the antibiotics consumption and the development of resistances (30). Lior et al. relate consumption differences to the national recommendations from pharmacotherapeutic guides, traditional treatments established in the culture of every country and different impacts of the pharmaceutical industry [27]. Vaccheri et al. points out a major consumption in the children and differences depending on the different sanitary systems and antibiotic policy that adopts each one [29].

**Factors associated with the infectious variability**

In this study we compared the prescription of antibiotics of systemic use in the population of our community, divided into 11 Health areas. The information of global prescription scarcely reflects the noticeable variations that they were found when the consumption is divided by areas. This showed the differences from 9 DID from the first one and the last that do not seem to match the geographical patterns, since on the one hand Salamanca, Avila, Zamora and Segovia presented the highest figures, whereas on the other hand, both areas of Valladolid,
Segovia and The Bierzo showed the lower consumption, keeping the areas of the north of the community with intermediate prescription figures.

To be able to analyze this geographical variability we must bear in mind the incidence of the infectious processes in which the use of this therapeutic group is indicated. We have resorted to the epidemiological bulletins of Castile and Leon from 2001 to 2005 where we observe the following points as relevant [32]: on the one hand diseases of obligatory declaration (DOD) that presented more incidence in Castile and Leon were the respiratory infections, followed by unspecific diarrhoea, flu and chicken pox. Among the infectious respiratory diseases the morbidity is caused by the acute respiratory infections (ARI).

A remarkable fact, the variation from year to year of ARI in our period of study showed a stable pattern with the exception of the year 2003 in which an important peak is observed (Figure 8) coinciding also with the peak of consumption this year.

Of remarkable interest is the information of ARI per province (Figure 9), highlighting those with a higher number of cases, such as Avila, Leon, Palencia and Salamanca, whereas Valladolid and Zamora were the provinces with the least incidence. It is important to indicate that in almost the whole community the cases declared in the year 2003 are superior to the rest of the studied period. A certain parallelism exists among the respiratory infection mentioned in the DOD with the information of prescription of antibiotics for the majority of provinces, ex-

**Figure 8 - Incident rate of acute respiratory infection in Castile and Leon from 2001 to 2005.**

**Figure 9 - Rate of incident of respiratory acute infection in the provinces of Castile and Leon in the period 2001-2005.**
cept for Zamora, which presenting the lowest figures of respiratory infection shows a high antibiotic consumption of systemic use. This discrepancy can be due to a wrong communication in the DOD because its rates are very low in a community with a very similar environment.

Flu is a disease that year after year produces epidemics in the countries of mild climate, affecting principally children and increasing the mortality among the elderly with chronic pathologies. Approximately 20% of the children and 5% of the adults can present influenza symptoms every year, though the patients’ proportion that comes to the sanitary system is lower, about 3% of the population in a normal epidemic. People over 65 are more seriously affected representing 90% of all the deaths attributable to the flu; it is not treated habitually with antibiotics, though in some cases, because of their bacterial complications or diagnostic difficulties they are used in this pathology. This is shown in the concordance of the flu peak in the year 2003 (Figure 10) with the maximum antibiotics consumption.

**Demographic factors**

Our community presents a highly number of people over 65, so that in some provinces it is over 25% such as Avila, Soria and Zamora, which is directly related to a high antibiotics consumption, especially quinolones, possibly due to a more incidence of urinary infections or respiratory low infections in this group of age and to its easy dosage, twice a day. Secondly, Zamora, Salamanca, Soria and Avila were the areas with a higher proportion of population under 14 years old and a bigger consumption of macrolides, whose probable reason might relate to a major incidence of otitis and sinusitis, which are the principal indications of this treatment.

One of the factors that seem to influence the prescription of antibiotics is the density of population. In this respect we obtained this information from the National Statistics Institute of the year 2006, where a low population density for the whole territory of Castile and Leon was estimated, though with important differences, between Soria with 9 inh/km² and Valladolid with a density around 64 inh/km². Leon, Palencia and Salamanca were between 25 and 50 inh/km² and the rest between 9 and 25 inh/km². Avila was the province that presented major geographical dispersion and we observed a certain parallelism with the major antibiotics consumption of a wide range, maybe related to the major low respiratory infections frequency in non urban zones and with superior access difficulty to medical services.

Related also to the demographic structure and with different results, Quarry et al. find major consumption in pensioners and Calvo et al. in the under 11-year-olds, and patients from 55 to 67 years old were of minor consumption [22, 33]. In a previous study in the province of Valladolid lower consumption in rural zones, related to the minor welfare pressure was observed [34].

**Other factors**

There are other reasons that might determine the variability prescription and that depend on

![Figure 10 - Evolution of the rate of the flu incident rate in Castile and Leon and in Spain.](image-url)
the sanitary system, like the number of physicians per inhabitant and the welfare pressure. Llor et al. supports that countries with a low number of doctors per inhabitant use more antibiotics, and that doctors with more time in the consultation and smaller number of assisted patients every day prescribe fewer antibiotics [27]. In fact they state that the time dedicated in the consultation to make clear to the patient that he does not need antibiotics is more than they need to write out the prescription for an antibiotic. On the other hand Coconut et al. do not justify this theory because they think that the used time is slightly superior when in a paediatric consultation an antibiotic is prescribed (14.24 minutes instead of 14.18 minutes on average if antibiotics are not prescribed), though a difference of a few seconds does not seem to be relevant [35].

Having valued the year to year evolution of the prescription volume for every area we highlight two relevant facts: first the important differences of prescription, and secondly the lack of peak consumption in Segovia and West Valladolid in the year 2003, which cannot be explained neither by its geographical nor the demographic information. These differences suggest the existence of a systematic and random variable. The systematic variable is present in the variation among doctors being employed in different areas whereas the random variable is present in the extreme variations inside the same area. If these variations cannot be explained either by variations of disease, or by medical resources, since it is such of the same sanitary system it would be more probably explained by other factors, such as individual perception of risk and beliefs on the benefits from the treatment that concern the relation patient-doctor.

Valuation of the prescription per area

The pattern of prescription observed in the health areas of our community was heterogeneous. The areas of Castile and Leon that presented the lowest figures of prescription were both areas of Valladolid, Segovia and The Bierzo, expecting for them an utilization in conformity to the recommendations from therapeutic guides, but we observed different facts in a more detailed analysis by means of therapeutic subgroups and active principles. Special interest is the analysis of both areas of Valladolid, for its physical proximity and minor differentiation of the environment. In spite of it we detect important differences of prescription, among them: West Valladolid showed an important consumption of amoxicillin-clavulanate in relation to amoxicillin, cephalosporins, especially cefuroxime and macrolides. In conclusion we might say that in spite of being the area with minor global prescription it presented an unbalanced consumption inside the geographical and demographic context of our Community. In the other side East Valladolid, with figures of consumption harmonic and balanced in the global context, only stood out for the high consumption of erythromycin. This fact makes us think that general use of antibiotics of systemic use is similar in both areas, but there are external factors that might be the object of subsequent analyses, such as welfare pressure, political management or activities of specific training that might modify the pattern of prescription.

In Segovia we observe a pattern of prescription more appropriate to the recommendations of the consensuses due to three relevant events: first the major prescription of amoxicillin in relation to amoxicillin-clavulanate, secondly, the low figures of prescription of cephalosporins and macrolides, especially azithromycin and cefixime, in agreement with its principal indications (otitis and sinusitis for the cephalosporins and allergies to penicillins of the macrolides) and thirdly (in opposition to previous settings) a higher consumption of sulfamethoxazole-trimethoprim, that presents very concrete indications. It was also paradoxical the information obtained in The Bierzo, with lower antibiotics consumption than other areas located in the north of Castile and Leon, with moderate and balanced consumptions of different subgroups and active principles. These finds from an area that works principally in a mountainous region might be explained for the difficulties of accessibility for the sanitary services when the climatological conditions are adverse, and cultural factors (beliefs, confidence in domestic remedies) would reduce the prescription.

The other areas in the north of the region (Leon, Burgos and Palencia) also showed significant differences in the pattern of prescription with intermediate figures of consumption. Burgos stood out for its high consumption of macrolides probably because it has the second index of infant-juvenile population. Soria, Salamanca, Zamora and Avila were the areas of major consumption; with figures around 20 and 22.5 DID, with great population dispersion and high indexes of dependence, so as for people over 65 year old and under 14,
highlighting a predominant consumption of a wide spectrum of therapeutic groups.

The different analyzed factors do not explain the variability prescription of antibiotics, so that other authors show different conclusions. At this point Lázaro et al. find uniformity, with a relative contribution of every therapeutic subgroup in all the autonomous communities of Spain, whereas other studies point out disparity in the pattern of antibiotics consumption, also inside the same province [2, 22].

Another important factor, not sufficiently analyzed, is the resistance to *Streptococcus pyogenes* and *Streptococcus pneumoniae* that show a geographical variability [36]. In this way, the areas of the north of Spain that took part in Perez Trallero’s study had the lowest rates of resistance, in relation with the different intensity of action produced by the diverse factors that influence the development of resistances, as the antibiotics consumption, the temporary flow of certain clones in a certain area and the seasonal fluctuations.

Key words: antibiotics, epidemiologic measures, demographics.
REFERENCES


