

Evaluation of antimicrobial use in the basic health units of Ponte Nova / MG

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ABSTRACT

Antimicrobials are prescribed drugs in large quantity in Primary Care. The use of these has been highlighted in the policies to rationalize the use of medicines, for being more consumed and because these are drugs most wrongly and abusively used. The study has as an objective to evaluate the process of antibacterial therapy in primary health care of Ponte Nova/MG, identifying the classes of most used antimicrobials, the main bacterial infections, comparing them to the indications to antibacterial therapy protocols. Field research was carried out in the Basic Health Units and in the Pharmacy of Minas, based on interviews guided by a survey, structured in a database with all the information collected through the program Epiinfo 7.2.1.0. Amoxicillin was the antimicrobial that appeared the most in the prescriptions, followed by cephalexin, ciprofloxacin and azithromycin. Among the most identified infections are the urinary tract and upper respiratory tract. Brazil and the European countries presented the same antimicrobial consumption pattern. The study illustrated the major problem currently presented, the considered increased risk of bacterial resistance, as it confirmed the abusive use of antimicrobials to treat infections.

Keywords: Antimicrobial; Bacterial Resistance; Primary Health Care

1 INTRODUCTION

The antimicrobials are substances that act on microorganisms by inhibiting his growth or causing his death, may having natural origin or synthetic (GUEDES;

ÁLVARES, 2014). This class of drugs is prescribed in large number in outpatient clinics and also is used as self-medication. This may cause an imbalance not only in the microbiota of the patient using it, but also in the microbial ecology of other patients(MOTA *et al.*, 2010).

The resistance might be intrinsic, when the resistance genes is part of the genetic code of the microorganism, being this predictable and constant, simply by knowing the scope of action of an antimicrobial to avoid it, or acquired, when the genes of resistance are not only present in the genetic code being incorporated into them, since this has a huge clinical influence because it is genetic alterations that may express biochemically, resulting on mutations in the bacterial chromosome or by the gene transfer from a cell to another(TAVARES, 2014).

Among the resistance acquisition mechanisms, we may quote the resistance acquired by mutation that may be caused by use of antimicrobials, especially when administered in subinhibitory doses. This mechanism happens after a failure during the DNA replication, forming different peptides by the derangement of the amino acid sequence. In this case the pharmaceutical is responsible in the selection of mutant cells (LIMA; BENJAMIM; SANTOS, 2017).

The bacterial can acquire also, external genetic charge through transferable resistance, by distinctive mechanisms, being them: *transformation*, the bacteria acquires free DNA that contains resistance genes and incorporates it its own genome; *transduction*, the bacteria act as a host of a virus, bacteriophage, in which transmit resistance genes during its reproductive cycle and *conjugation*, a kind of bacterial reproduction in which occurs transmission of resistance elements through plasmids, that may contain resistance genes to antimicrobials and exists freely in the organism or integrate bacterial chromosomal DNA, and through transposons, that may be inserted previously in plasmids and/or bacterial

chromosomes and being transferred between bacterias (LIMA; BENJAMIM; SANTOS, 2017).

And finally induced resistance, being the induction a genetic phenomenon that results from the liberation of genes responsible by a determined cell characteristic that was repressed by another gene producer of a repressive substance (TAVARES, 2014).

There is also the possibility of the bacteria to acquire resistance through biochemical mechanisms through the *enzymatic inactivation*, main mechanism of bacterial resistance, when these promotes the transfer of chemical groups or have hydrolytic activity, such as the known β -lactamases which cleaves β -lactam rings of penicillins and cephalosporins, triggering the loss of antimicrobial function (OLIVEIRA; SILVA, 2008); change in drug permeability, mechanism that changes the structure of membrane making it impossible for the antimicrobial to act in its place of action as it is unable to cross the lipopolysaccharide outer membrane of gram-negative germs (COSTA; SILVA JUNIOR, 2017); modification of transport systems in the cell that may appear through mutations that affects the energy metabolism of the membrane, thus reducing the potential difference across the membrane and reducing the penetration of antimicrobials, which are dependent on active transport and only occur in aerobic conditions (BAPTISTA, 2013); active withdrawal of the drug from the intracellular environment, also known as efflux of cell antimicrobials that exports the antimicrobials to the extracellular environment, this mechanism is also dependent of energy and are not specific, may working for antimicrobials from different classes (COSTA; SILVA JUNIOR, 2017); drug receptor change, this mechanism is acquired through chromosomal mutation, checking a decreasing of affinity of antimicrobials by the receptor proteins, and finally the modification of the active metabolic system for the drug and synthesis of alternative metabolic pathways configured by changes in the enzymatic system of

nucleic acid synthesis based on a metabolic sequence of folic acid derivatives, in which participates different reductase and synthase that can be inhibited by antimicrobials (TAVARES, 2014).

It is worth to emphasize that the chromosomal resistance depends from spontaneous mutation, a rare event, as it is directed almost always to only one drug, so considering the clinical aspect the plasmidial resistance has more importance (ANTONIO et al., 2009).

We must consider the relation between bacterial resistance, the misuse of antimicrobials and the growing infections with therapeutic difficulties and therefore difficult treatment of the infections leading to greater lethality, which is no longer an individual problem but a collective problem. Besides that, each day decreases even more the barrier between the hospitals and the community, increasing considerably the most serious infection rates at Community level (ZIMERMAN, 2010).

Therefore, the study aimed to evaluate the process of antibacterial therapy in Primary Health Care of Ponte Nova/MG. For such it was made the following steps: identification of the classes of most used antimicrobials, the main bacterial infections treated with antimicrobials and it compared after evaluation of prescriptions the correlation between the clinical indication and the use of antimicrobial.

2 METHODOLOGY

The field work was made in the Basic Family Health Units (UBSF), where acts Family Health Strategies (ESF) and in the Minas Pharmacy in the municipality of Ponte Nova/MG, Zona da Mata Mineira. It has an estimated population of 59,742 inhabitants for 2019 (data from IBGE, 2010) and 23 healthcare facilities with outpatient care, being 16 UBSF, of these 11 with action of ESF, totalizing 13 active

teams and 78% of total area of city with team coverage. It was made in this investigation a descriptive, observational field research based on a population-based cross-sectional study through interviews guided by a structured questionnaire. It was included all the users of Health Primary Care of the city attended in UBSF with acting on ESF, attended in the same week as the interview with prescribed antimicrobials and that uses the services of Minas pharmacy, in other words, the users attended by SUS and that uses antimicrobial drugs dispensed by SUS.

The participation was voluntary and linked to express approval of the subject through the signature of the Informed Consent Form, when the patient was above 18 years old and the Term of Consent, if the patient were under 18 years old, being in this case respected the established norms in the Child and Adolescent Statute (ECA). When the child or adolescent needed to sign the Consent Form, this did not release the signature of the person responsible for the Consent Form. This research was approved by the Ethics and Research Committee of the Federal University of Viçosa, according to opinion 2.205.382.

It was made an interview guided by a survey for data collection of socio-demographic information (gender, age, level of education, neighborhood of residence), clinics (identification of the prescribed antimicrobial, dosage, length of treatment, mode of use and diagnosis determined by the prescriber) and clinical conduct (anamnesis and physical examination). These data were compiled later and it was made a study to check the correct use of antimicrobials. The data were analyzed by the programs Epiinfo 7.2.1.0 and Microsoft Office Word[®], Excel[®] 2011.

3 RESULTS

It was made 314 interviews in the 13 USBF and in Minas pharmacy, at the time of the prescription with dispensation of the antimicrobials, during the months of October/2017 and February/2018. The following antimicrobials prescribed in the

Basic Health Units analyzed in this study were found, in descending order of frequency that appeared in the prescriptions (Table 1).

Table 1 – Antimicrobials prescribed in the Basic Family Health Units, Ponte Nova, Minas Gerais, 2018 (n = 314)

Variables	N	%
Prescribed Antimicrobials		
Amoxicillin 500mg capsule	76	24.20
Cefalexin 500mg tablete	48	15.29
Ciprofloxacino 500mg tablete	48	15.29
Azithromycin 500mg tablete	37	11.78
Amoxicillin + Clavulanate tablet 500 / 125mg	33	10.51
Metronidazole 250mg tablete	23	7.32
Cephalexinsuspension	7	2.23
Norfloxacin 400mg tablete	7	2.23
Amoxicillin 250mg / 5mL suspension Fr 150mL	6	1.91
Sulfamethoxazole + Trimethoprim 200 + 40mg / 5mL suspension	5	1.59
Metronidazole vaginal jelly	4	1.27
Sulfamethoxazole + Trimethoprim 400 + 80mg pill	4	1.27
Amoxicillin + Clavulanate suspension Fr 75mL	3	0.96
Azithromycinsuspension	3	0.96
Clindamycin 300mg tablete	3	0.96
Nitrofurantoin 100mg capsule	3	0.96
BenzathinePenicillin 1,200,000UI Bottle	2	0.64
Doxycycline 100mg tablete	1	0.32
Metronidazole 4% suspension	1	0.32
TOTAL	314	100.00

Source: Authors (2020)

By evaluating the use of antimicrobials separated by therapeutic classes, we observed that 38.85% (n=122) of the of the prescriptions received in the interviews, contained a penicillin; the quinolones, represented in this study by ciprofloxacin, nitrofurantoin and norfloxacin, appeared in 58 (18.47%) of the prescriptions.

Cephalosporins, represented exclusively by cephalexin in this study, were prescribed in 17.52% (n=55) of the situations evaluated in the period of the study. Were also prescribed antimicrobials from the class of macrolides (erythromycin, clarithromycin and azithromycin) in 38 (12.10%) prescriptions.

Among the health problems observed, the most identified were the urinary infection (n=57 / 18.15%) and pharyngoamigdalitis (n=34 / 10.83%). Among these, are the infections undefined that were classified due to the ignorance of the patient interviewed regarding the problem associated with his antimicrobial treatment, thus not being discussed in this study. Still were quoted the otitis (n=9 / 2.87%) and sinusitis (n=8 / 2.55%), upper respiratory tract infections.

Between the interviews 81 (25.83%) patients said that they treated with antimicrobials, problems that were not associated to the bacterial infections, however considered as a mistake in drug indication and so classified in the analysis as "others". For example, virosis (n = 15 / 4.78%), oral dental inflammation (n = 11 / 3.50%), worms (n = 8 / 2.55%) and allergy (n = 3/0), 96%).

It was found for treatment for urinary infection, the biggest use of ciprofloxacin 500mg tablet, in the dose of 1 12/12 hour tablet, during 7 days (n=18 / 31.58%) during five days (n=8 / 14.04%). For patients which were diagnosed with pharyngoamigdalitis were prescribed, mainly the azithromycin 500mg tablet, to be given one 24/24 hour tablet for five days (n=8 / 23.53%), but also were prescribed the amoxicillin 500mg tablet with a dosage of 1 tablet 8/8 hours for 7 days on 5 prescriptions (14.71%). Cephalexin 500mg tablet was used in the dosage of 1 tablet four times a day for seven days (n=5 / 17.86%) and ten days (n=4 / 14.29%) for treatment of dermatological infections represented by the wound. Taking into account the treatment of upper respiratory tract, appeared in the prescriptions the antimicrobials amoxicillin 500mg and amoxicillin + clavulanate 500/125mg for otitis and sinusitis, and the latter in suspension for sinusitis, azithromycin in suspension for otitis and in tablet (500mg) for sinusitis and otitis, and also sulfamethoxazole + trimethoprim 200 + 40mg/5mL for the treatment of otitis.

Another aspect evaluated in the study made in Primary Care was the quality of the prescription as to its necessary and sufficient informative aspects for the good understanding by the patient, thus ensuring its rational treatment. It is worth remembering that were not evaluated the ethical aspects.

In only 14 (4.46%) prescriptions, from 314 evaluated, were not informing the total amount of the antimicrobial for the full treatment. The presence of informations in the prescriptions it is not a guarantee that the patient will understand the content, by several reasons, being one of them, the illegibility that brings to the patient the difficulty to obey to the dosage system set out in the prescription.

It is important to highlight that in this point of the interview, the patients could choose more than one option, unless it has an answer "nothing" or "don't know how to read" those being single-marked. So, we can notice that in the total of 314 prescriptions analyzed, in 66 (21.02%) the patient did not understand any information contained in this. Other 75 (23.89%) and 82 (26.11%) did not understand the name of the medication and the full dosage, respectively. And in only 31 (9.87%) of the prescriptions attended had other information and were understood by it, between these we can quote the time of administration of the antimicrobial, how it should be administered (fasting or not, for example) and the route of administration.

Among the orientations transmitted to the patient during the appointment, were quoted the following ones: "how to use", "when to use", "for how long to use", "possible collateral damage" and "precautions" Yet, it has existed the possibility of not having received any information about the prescriber, being that, in this aspect 101 (32.17%) of the patients identified themselves with this option. Considering the other options, more than half of patients were not guided and only 6 (1.91%) were informed about the possible collateral damages that the antimicrobial may present during the treatment.

4 DISCUSSION

The use of antimicrobials in Brazil, presents itself a similar picture to that of Europe. Penicillins are the most widely used class in the community in all European countries, represented by 30% consumption in Germany to 67% in Slovenia. Between other classes are also widely used, as observed, in this study, are the cephalosporins and quinolones. Amoxylicin (40.1%) and cephalexin (13.6%) were also the antimicrobials more used in researches made in Jatai (GO), where it was based in the same methodology used in this study, the interviews made guided by a survey, thus confirming the high use of penicillins and cephalosporins in prescriptions for community infections (BRAOIOS *et al.*, 2013).

We can also observe that in the study of Ramalhinho *et al.* (2015), the most prescribed class was the penicillins highlighting amoxicillin + clavulanate and amoxicillin. Sequentially, the macrolides and quinolones, respectively had a higher frequency in the prescription analyzed. Among the classes that were most prescribed in this study, we have the penicillines, being the amoxylicin 500 mg the most prescribed, and the cephalosporins with a first generation representative (cephalexin 500mg), as the only representative of this class identified in this study. We can still consider that, among the macrolides, the preference for the prescription of azithromycin, is related probably with better pharmacokinetic properties, more comfortable dosage and less adverse effects, when compared with others in the same group such as erythromycin (RAMALHINHO *et al.*, 2015).

According to the study of Nicolini *et al.* (2008), the high consumption of cephalosporins must be a matter of concern, because it is one of the causes of bacterial resistance, being that cephalosporins of first generation (cephalexin) are less concern than the use of the second or even the third and fourth generations (NICOLINI *et al.*, 2008).

About the use of quinolones in the treatment of community urinary infections, we observed through studies that the high consumption of this class is

related to the higher risk of resistance in *Escherichia coli*. This finding illustrates the correlation between human population consumption of antimicrobials and individual bacterial resistance. Thus, the increase of using of a determined antimicrobial in human population of a city has a direct relation with the rise of individual resistance and with alterations in microbial population in that area of influence (CAMARGO *et al.*, 2012).

Still, about the research made on Jataí (GO), were identified the major prevalence of oropharyngeal infections (29.5%), dental treatment (13.6%) and urinary/renal infection (13.6%) being causes of antimicrobial use. In the present study, these also appeared in the analysis of the results among the group of the most diagnosed in the subject of the research.

In the study of Ramalhinho *et al.* (2015), with the population of Algarve in Portugal, from the 964 indications that motivated the prescription of antimicrobials, the most prevalent infections were those associated to the respiratory tract, urinary tract, digestive tract, skin, ear and other infections respectively. Similarities can be observed with the present study, by identifying that the infections quoted above were also the ones that appeared the most in the analysis of the results, with exception of digestive tract that has not shown significant frequency.

We can consider that, in this study, the highest prevalence of infections from urinary tract is due to the higher frequency of female gender (n=214 / 68.15%) in the study participation, this fact can be assigned to the difference of incidence of urinary tract infections, and also, because of the period that the interviews were carried out, during the months of October/2017 and February/2018, high summer, in which the respiratory tract infections are less frequent. We suspect that in all infections from urinary tract, presented in this study were in women premenopausal, sexually active, immunocompetent and non-pregnant, community acquired. Thus, it is convenient to associate the infection to *Escherichia coli* and the therapy can be established without necessity and urine examinations (TAVARES; MARINHO, 2015).

It was identified in the study that the most used drug in the treatment of urinary tracts was the ciprofloxacin, first line fluorquinolone in cystitis therapy because they have great antimicrobial activity against enteric gram-negative bacilli. The most used dosage in the identified medical conduct was the use of 1 tablet of 500mg of 12/12 hours, during 7 days. The dosage of usual ciprofloxacin to fight this infection is 1 tablet of 250mg 12/12 hours, for 3 days (TAVARES; MARINHO, 2015). Considering so, this pattern in the treatment of urinary tracts, the study shown us a higher concentration of the drug during a period far above recommended. Even if we consider the long-term treatment of urinary tract infection, the recommended drug is nitrofurantoin, which appeared in a prescription of the 57 identified for the treatment of this type of infection.

Therefore, for the empirical antimicrobial selection for non-complicated acute cystitis, we must consider the local antimicrobial susceptibility of *E. coli* in particular. Thus, the ciprofloxacin shown high resistance levels in studies made in North America and Europe and there has been a trend of increasing of this resistance through time (HOOTON; KALPANA, 2018).

From the urinocultures evaluated in a study made in the county of Divinópolis/MG, 72.8% isolated the *E. coli* bacteria, being 38.6% of them resistant to Sulfamethoxazole + trimethoprim, 33.0% norfloxacin, 31.8% ciprofloxacin and 9.0% nitrofurantoin, which justifies the choice of the latter (FERREIRA et al., 2017).

In this study we observed that the prevalence in the treatment of the pharyngotonsillitis was with the azithromycin 500mg, 1 tablet, once daily, for 5 days (23.53%), followed by Amoxylicin 500mg, 1 8/8 hour tablet, for 7 days (14.71%) and for 10 days (11.76%). It suggests that the prescribers chose to increase the chances of an effective treatment, betting in a short-term treatment with macrolides. According to Tavares and Marinho (2015), penicilines still being the drug of choice for the treatment of the pharyngotonsillitis, presenting 3 to 5% of clinical failures with the amoxicillin against 5 to 10% with the azithromycin.

In Brazil, the middle ear viral infection is quite common, being described in up to 57% of the cases where there was no bacterial growth and even 45% of the cases with proven bacterial infection. According to international studies the main bacteria involved in the Acute Otitis Media (AOM) are: *Streptococcus pneumoniae* (20% to 40%), *Haemophilus influenzae* (15% to 30%), *Moraxella catarrhalis* (10% to 20%), *Streptococcus pyogenes* and *Staphylococcus aureus* (2% to 3%). In the AOM, the natural history proved that the spontaneous resolution happens in more than 80% of the cases, with improvement without antimicrobial. The amoxicillin 500mg via oral 8/8 hours, remains the treatment of choice for OMA and in the recurring OMA recommends broad spectrum antimicrobials, such as amoxicillin associated to clavulanic acid 500 / 125mg orally 8/8 hours. The length of the treatment must be minimum 10 days.

The treatment of bacterial sinusitis varies in different places, but it defines itself in amoxicillin in usual doses and the association of amoxicillin in higher dose with clavulanate, cephalosporins and macrolides (SIH; BRICKS, 2008).

The choice of the antimicrobial agents should prioritize the infection caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, considering its prevalence. Thus, the treatment resumes itself in amoxicillin 500mg orally 8/8 hours during 7 to 10 days and as second choice increased doses of amoxicillin or amoxicillin 500mg associated with 125mg clavulanate, for 7 to 14 days, with an interval between doses of 8 hours (TAVARES; MARINHO, 2015).

In relation to the references quoted above, we can say that there was a coincidence by comparing its results to the ones in the present study prevailing in this last one the amoxicillin 500mg, three times a day during 7 days (25.00%) and 14 days (12.50%), followed by amoxicillin + clavulanate 500/125mg, also 8/8 hours, during 7 days (25.00%).

In a study made in the city of São Paulo, 68% of the antimicrobials prescribed to children under 7 years old with acute respiratory infections were inappropriate. The major problems found in the treatment of the otitis and tonsillitis were the

choose of broad spectrum antimicrobials, short-term treatment, errors in the interval between doses or prescription of ineffective antimicrobials for the eradication of oropharyngeal bacteria. The *Streptococcus pneumoniae*, the main agent associated to airborne infections, increased their levels of resistance to penicillin derivatives from 2.5 to 13% (DEL FIOLE *et al*, 2010).

National consensus and established international protocols has recommended 10-day uninterrupted therapy regimens for otitis and sinusitis (DEL FIOLE *et al*, 2010). In the present study in otitis, the average prescription time (4.8 days) was far below recommended and in the sinusitis this average time was from 6.8 days, also far below recommended considering this, an important variable when it comes to the increased risks of bacterial resistance.

Considering the otitis and sinusitis, there is the major possibility of being associated to associate with viral etiology infections. Even in case of diagnosis of bacterial infection there is the possibility of being treated with clearance and drainage measures for respiratory secretions. Thus, we must consider that in the context of ESF action-oriented focused on actions of promotion, protection and recovery of family health, in an integral and continuous way, the prescriber is able to analyze and monitor the patient, in order to only prescribe antimicrobials for such diseases in exceptional situations, being able to use more careful and rational behavior (TAVARES; BERTOLDI; MUCCILLO-BAISCH, 2008).

In a research made in the city of Imperatriz/MA, in 2014, about the prescription errors in antibiotic therapy, we observed in the results that in 83.7% of the prescriptions analyzed were identified the total amount of medicine for the treatment, similar result to the one presented in this research that in 95.5% of the prescriptions had this information (MARTINS *et al.*, 2014).

Still considering this study in the city of Imperatriz, the frequency of administration was present in 100% of the prescriptions analyzed, in this research, 23.89% did not present the name of the drug and 26.11% did not present the complete dosage.

We can compare the data analyzed regarding to the understanding of treatment dosage, that in this study 26.11% of the patients did not understand this aspect and the data presented in a study made in a public pharmacy in the western region of the city of São Paulo, where 15.44% of the patients did not understand the dosage. This fact may compromise the treatment and increase the risk of a bacterial infection (NICOLINI *et al.*, 2008).

According Del Fiol *et al.* (2010) the amount of information transmitted to the patients in the moment of the appointment is one of the limiting factors when it comes to rational use of antimicrobials. In this research we can observe a certain lack of this information, where were identified in the interviews that 67.8% of the patients did not receive any information about the treatment with the prescribed antimicrobial and in 100% of the interviewed was identified lack of information about the antibiotic therapy precautions. To try to minimize all the problems related to misuse of antimicrobials, one of the measures would be guarantee that the patient has total comprehension of the proper and safe administration (NICOLINI *et al.*, 2008). So, all of these aspects analyzed in relation to the information transmitted to the patient during the appointment, as well as the possible side effects, for how long to use, when to use, how to use and the precautions, becomes of extreme relevance considering this factor as limiting in the adequate use of antimicrobials.

5 CONCLUSIONS

The bacterial resistance is seen as one of the major problems of public health in the world, being that each day we can notice the acceleration of that process that should have been eradicated. This is due to the fact of the very evident correlation of the higher consumption of antimicrobials associated with higher levels of microbial resistance. This study confirmed the abusive use of antimicrobials for treatment of infections as the cause of the big problem presented

nowadays in the world, the increase of bacterial resistance. It can still be observed that besides the high frequency in the use of these medicines, there was a great diversity of antimicrobials with distinctive dosages for treatment of a single infection, often differing from previous official protocols and publications on the treatment of various bacterial infections at community level.

The bacterial resistance will always be a problem to be fought and to be world concern, even if the frequency of use of antimicrobials is reduced, because the simple exposure to these drugs is enough to initiate a resistance process.

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