

RESEARCH ARTICLE

General practitioners of the town of toamasina facing antibiotherapy in child and antimicrobial resistance.**Andry Maharo Andrianarivelo^{1*}, Arthur Bien Aimé Ratsimbazafy², Miora Tantely Rasamindrakotroka¹, Lalaina Mamenosoa Rakotondraolina¹, Annie Armandine Raharisoa¹, Andry Rasamindrakotroka¹.**¹Laboratory of Training and Research in Medical Biology, University of Antananarivo, Madagascar.²Department Mother and Child, Faculty of Medicine Toamasina, Madagascar.**ABSTRACT**

The main actor of antibiotic prescription in medicine in town is the general practitioner. The excessive consumption of antibiotic is a major public health problem, which participate in the emergence of resisting bacteria. This study was undertaken to evaluate the knowledge of the general practitioners in the town of Toamasina (Madagascar) about the use of antibiotics in children as well as their knowledge of multidrug-resistant bacteria so as to improve the daily practice.

It is about a prospective study, transversal and analytic done in the liberal general practitioners of the town of Toamasina concerning their knowledge on the antibiotic prescription in child as well as their perception and knowledge on the multidrug-resistant bacteria, by means of practical questionnaire.

Ninety six doctors agreed to answer the questionnaire. Doctors almost always prescribe antibiotics in the presence of an infectious syndrome. The amoxicillin and the amoxicillin + clavulanic acid association have been the most prescribed molecules prescribed by the doctors. Seventy percent of the general practitioners questioned have faced antimicrobial resistance and 48% said that they had difficulty. It appeared that the doctors didn't know the MRSA as well as the VRE or the ESBL or the CPE ($p < 0.05$). When they knew the CPE, they knew the VRE and the ESBL ($p < 0.05$).

The prescription is not justified in some cases and that the molecules chosen by the general practitioners do not correspond to the suspected pathology. It is registered in a rich context of actuality on the need of the implementation of a national program so as to improve the good use of antibiotics, especially in town, to limit the emergence of resisting bacteria, with the main goal to elaborate documents of references about the prescription of antibiotics. The antimicrobial resistance is a real problem of public health but which still seems to be too abstract for the general practitioner in Toamasina.

INTRODUCTION

The main actor of antibiotic prescription in medicine in town is the general practitioner. In spite of the pressure of selection that they induce and the occurrence of inflammatory state, the antibiotics remain precious drugs. Their excessive consumption is a major public health problem, which participate in the emergence of resisting bacteria or the decrease of sensibility to the antibiotics of international dimension. That report leads the infectiologists and the sanitary authorities in several countries to recommend more reasonable use of antibiotics by the implementation of campaign of information in national plan, as well as international. Or, every bacteria might get a capacity to acquire resistance to antibiotics. So, the repeated and accurate intake of antibiotics can lead to the emergence of resistant bacteria that will make subsequent antibiotics less effective for the patient in whom they appear, but also for the community when they diffuse into the environment and are transmitted to other patients [1].

However, before taking suitable actions for their good

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use, the status report of their use is essential. That report has been done in most of developed countries [2, 3]. However, in developing countries like Madagascar, the use of antibiotics in child in medicine in town was very little studied as well as knowledge of general practitioners regarding multidrug-resistant bacteria.

This study was undertaken to evaluate the knowledge of the general practitioners in the town of Toamasina (Madagascar) about the use of antibiotics in children as well as their knowledge of multidrug-resistant (MDR) bacteria so as to improve the daily practice.

METHODS

It is about a prospective study, transversal and analytic done in the liberal general practitioners of the town of Toamasina concerning their knowledge on the antibiotic prescription in child as well as their perception and knowledge on the MDR bacteria, by means of practical questionnaire. The survey has been done in the office of the doctor and in an anonymous way. Our study has been realized in a 3 months period from June to August 2018. The answers of all the doctors who have agreed to answer the questionnaire have been included. The variables selected and studied were the antibiotic treatments prescribed by these physicians in the event of a probable

infection, as well as their knowledge about multidrug-resistant bacteria. The data have been treated and analyzed with the software stata 11, Epi info version 3.5.4. The threshold of significance chosen was fixed to $p < 0.05$.

This study respected the standard regarding the ethical consideration particularly the enlightened consent, the confidentiality, the professional secrecy, the human rights. Before any participation to the study, each doctor has been informed about the goal of the research. During the interview, each participant has the right to withdraw whatever the reasons.

Concerning the limits of the study, our population is not representative of all the doctors in Toamasina or Madagascar and might be distorted by uncertainty of answers given by the participants.

RESULTS

Ninety six doctors agreed to answer the questionnaire, 13 doctors refused to participate to the study. Among the 96 general practitioners who answered, we identify 54 women (56.25%) and 42 men (43.75%). All of the doctors (96) had isolated method of exercise.

The doctors always prescribe antibiotics during the acute otitis media, urinary infection, and feverish gastroenterite. Ninety one and eighty one doctors prescribe antibiotics concerning respectively community pneumonia and cutaneous infection. The amoxicillin + clavulanic acid association (47.91%) has been the most prescribed antibiotics during the acute otitis media, the amoxicillin (52.08%) for the community pneumonia, the ciprofloxacin (29.16%) followed by the amoxicillin + clavulanic acid (26.04%) for the urinary infection, the metronidazol (56.25%) for the feverish gastroenterite and the oxacillin (23.45%) followed by the fusidic acid (20.98%) for the cutaneous infection (Table I).

The amoxicillin and the amoxicillin + clavulanic acid association have been the most prescribed molecules prescribed by the doctors followed by ciprofloxacin and ceftriaxon (Table I). The antibiotics have been prescribed by monotherapy in 96% of the cases and administrated orally in 89% of the cases.

Concerning the duration of the antibiotherapy, it varies from 3 to 10 days, with a median of 6 days. The posology are varied depending on the doctors and the results are not significant. Twenty three percent of the general practitioners prescribed bacteriologic analysis and 45% proved to be positive.

Seventy percent of the general practitioners questioned have faced antimicrobial resistance and 48% said that they had difficulty. There was no significant difference statistically between the knowledge of multidrug-resistant bacteria and the confrontation to antimicrobial resistance problems.

That question evaluated the knowledge of the multidrug-resistant bacteria by the general practitioners. In 80.20% of the cases, the doctors knew the MRSA. The CPE and the VRE are the multidrug resistant bacteria that they didn't know so much in respectively 84.37% and 78.12% of the cases. It

appeared that the doctors didn't know the MRSA as well as the VRE or the ESBL or the CPE ($p < 0.05$). When they knew the CPE, they knew the VRE and the ESBL ($p < 0.05$) (Table II). The general practitioners of less than 35 years knew the VRE ($p < 0.05$) and the older than 55 didn't know the ESBL ($p < 0.05$). Ninety seven percent of them haven't done ongoing medical training concerning the multidrug resistant bacteria and 96% of the general practitioners questioned didn't know the causes of the development of antimicrobial resistance.

DISCUSSION

The prescription of antibiotics must lead to therapeutic effectiveness. For this to happen, a correct antibiotherapy is based on the knowledge of both bacteriologic germ data responsible of the infection, the pharmacokinetic of the antibiotics and of the awareness of the field. The appearance of resistance is caused by the overconsumption of antibiotics and of their misuse (short treatment or too long and sometimes with incorrect dosage) which lead to the emergence of the development of resisting bacteria towards the antibiotics [4, 5]. This main public health problem has raised the worldwide awareness of the emergency to find their right use [4, 6]. In France, more than 90% of antibiotic prescriptions are made in town whom 70% are by the general practitioners [7, 8, 9]. During the study period, 96 general practitioners agreed to answer the questionnaire. They have treated all the cases of AOM with antibiotics whereas the roles of the viral infections could not be rejected. In most of the cases, those infections are viral [10]. The viruses are the causes of the extended evolution of the AOM, with a slower healing and more frequent recurrence. They could be responsible of failure of antibiotherapy [9]. The ORL infections are the most frequent infections of the children and the first causes of antibiotic prescription, according to some authors [10]. The prescription of antibiotics has been dominated in 47.91% by the amoxicillin + clavulanic acid association during the AOM (table I). According to the literature, in most of the cases, the initial AOM treatment is probabilistic, and facing apurulent otitis, the choice was focused on the amoxicillin + clavulanic acid association, a cephalosporin of second or third generation orally [9]. As for the AOM of the children of less than 2 years, as the recommendation of the Society of Infectious Pathologies of French Language, initial therapeutic abstention is recommended, with reevaluation of 48 to 72 h in case of clinic table not so severe. The antibiotic is recommended right away in front of a noisy symptomatology (fever, otalgia), difficulty of understanding of the patient or during the reevaluation in 48 hours in case of persistence of symptoms [6].

The low respiratory infections including community acquired pneumonia represent the second cause of antibiotic prescription [10]. In our study, the doctors have prescribed antibiotics in 91 children concerning the CP and the amoxicillin has been the most prescribed (54.94%) (Table I). The vast majority of those infections

Table I : Distribution concerning to the antibiotics prescribed according to the types of diseases.

Antibiotics	AOM		CP		UI		FG		CI	
	n	%	n	%	n	%	n	%	n	%
Amoxicillin	17	17.70	50	54.94	17	17.70	8	8.33	6	7.41
Amoxi-clav	46	47.91	27	29.67	25	26.04	-	-	12	14.81
Cefixim	14	14.58	-	-	-	-	6	6.25	-	-
Ceftriaxon	-	-	9	9.89	11	11.46	9	9.37	-	-
Ciprofloxacin	6	6.25	-	-	28	29.16	8	8.33	-	-
Cotrimoxazol	-	-	5	5.49	15	15.62	-	-	-	-
Oxacillin	-	-	-	-	-	-	-	-	19	23.45
Fusidic acid	-	-	-	-	-	-	-	-	17	20.98
Erythromycin	-	-	-	-	-	-	-	-	10	12.34
Metronidazol	-	-	-	-	-	-	54	56.25	-	-
Others	13	13.54	-	-	-	-	11	11.46	17	20.98
Total	96	100	91	100	96	100	96	100	81	100

Amoxi-clav: amoxicillin + clavulanic acid, AOM: acute otitis media, CP: community pneumonia, UI: urinary infection, FG: feverish gastroenterite, CI: cutaneous infection

Table II : Knowledge about multidrug resistant bacteria by general practitioners.

M D R	N o		Y e s	
	n	%	n	%
M R S A	19	19,8	77	80,2
E S B L	33	34,38	63	65,62
C P E	81	84,37	15	15,63
V R E	75	78,12	21	21,88

MRSA: Methicillin resistant *Staphylococcus aureus*, ESBL: Extended spectrum beta-lactamases, CPE: carbapenemase producing Enterobacteriaceae, VRE: Vancomycin resistant Enterococci

are of viral origin and the natural evolution is mostly done through spontaneous healing [11]. The goals of antibiotherapy are to cure the evolutive infection or a viral disease superinfected. It must strictly be given to young children and/or having clinical severity criteria or radiologic and when there is an underlying pathology. As for the literature, a betalactamin is suggested at the forefront: amoxicillin, amoxicillin + clavulanic acid or oral cephalosporin [9]

The urinary infections represent the most frequent cases of bacterial infection documented in children [12]. In our study, during the UI, the doctors always prescribe antibiotics which the ciprofloxacin (29.16%) followed by the amoxicillin + clavulanic acid have been the most prescribed (table I). According to the literature, the treatment is suggested to sterilize urine and make the functional gene disappear. It is based on active antibiotics orally taken, well tolerated, of weak toxicity and might reach an active effective urinary concentration on the germ. The possible molecules are aminopenicilin or cephalosporin. The fluoroquinolones don't have the marketing authorization in pediatrics and the nalidixic acid is contraindicated before the age of one year because of the risk of intracranial high blood pressure and metabolic acidosis [9].

The gastroenteritis mostly of viral origin, Norovirus and Rotavirus the most frequent virusin cause in young children. Among the bacterial causes, few of them need antibiotics treatment except shigellosis, serious form of salmonellosis and of some campylobacter infections [9, 13]. Doctors always prescribe antibiotic during the FG in our study and the metronidazole (56.25%) was the most prescribed antibiotics (Table I). Some authors recommend azithromycin, ceftriaxone and ciprofloxacin for the rare cases which must be treated by antibiotics [13]. The empirical treatment without bacterial identification are rarely indicated outside sepsis grave or in risky subject [13].

The bacterial cutaneous infections are frequent in children and doesn't always need antibiotherapy by general route especially in superficial form [14]. In our cases, 81 doctors prescribe antibiotics and oxacilline (23.45%) followed by fusidic acid (20.98%) which has been the most prescribed. As for the literature, associated by the local treatment (antiseptic ± antibiotics), in first intention, we choose a betalactamin (oxacillin, clavulanic acid and amoxicillin association) a cephalosporin of first generation or a macrolid [9]

The consumption evolves qualitatively as well (table I). The penicillin with large spectrum are increasingly used, as well as amoxicillin associated with clavulanic acid, in which the prescription are all the more worrying that those antibiotics are particularly among the antibiotics which generate resistances. However, the consumption of cephalosporin is minor. Contrary to other country, the cephalosporins of first and second generation are not used by the doctors [1].

The duration of antibiotherapy that the general practitioner suggested with a median of 6 days and change from 3 to 10 days was not in accordance with the recommendation which is 8 to 10 days [9]. In 2015 was published in France the Carlet report "Tous ensemble,

sauvons les antibiotiques" which suggest new measures aiming to control this phenomena, especially by decreasing the duration of prescription [15]. As for that report, it suits to limit the duration of the initial prescription of an antibiotics in town to 7 days at maximum, because the majority of infections met in ambulatory medicine doesn't need more than one week of antibiotherapy. Moreover, a recent work of the Society of Infectious Pathologies of French Language was led to suggest the shortest duration of treatment [16]. The antibiotics prescription is based on precise diagnosis, based if possible on rapid diagnosis test, otherwise a probabilistic treatment referring to the bacteria etiology the most probable; the characteristic of the patient (age, weight, liver and kidney function, fragility): a spectrum of the antibiotics which is the closest possible and the shortest duration of treatment possible so as to avoid the selection of resisting strain [17].

The antibiotics have been administered orally in 98% of the cases. As for some authors, for the patient which are not admitted to hospital, the oral route is the standard. It must be used right away in the absence of severity of clinical sign. The antibiotics available orally having a bio equivalence IV/per os are the following: fluoroquinolones, metronidazol, tetracyclin, cotrimoxazol, linezolid, and of least degree of amoxicillin [18]. It is recommended to favour the oral route, avoid to prescribe the same antibiotic or the same class in three months of precedent use on the same patient, to respect the posology and the duration of recommended treatment and to re-evaluate the effectiveness of the antibiotics treatment on the symptoms between 48 and 72 hours after the beginning of the treatment [9, 17, 19, 20]. The decision to prescribe an antibiotic must be rational. An antibiotic must be strictly contra indicated, when it is not strictly indicated. The optimization of antibiotics prescription goes through a long term education beside the public: we should admit that not all the fever are infectious, that not all the infections are from bacteria, that all the bacterial infections does not compulsory justify an antibiotics treatment and the in a lot of cases, the antibiotics treatment is not an emergency. What might be urgent on the contrary is to make diagnosis [21].

In our study, more than 70% of the general practitioners questioned have been confronted to antimicrobial resistance and that half of them said having difficulties. There was a multicentric study lead in Europe in 2012 which said that the general practitioners estimated the antimicrobial resistance as more important in the country globally than individually [22]. This allows us to say that the antimicrobial resistance problem really exist in medicine in town of Toamasina and even in all the country. Those problems would become more serious without improvement of the good use of the antibiotics and without the discovery of new molecules [22]. The better would be to have data about the antimicrobial resistance locally as Pulcini and al and Simpson and al have already suggested [23, 24].

Almost the entire doctors have not done ongoing medical trainings concerning the MDR bacteria and don't even know the causes of the development of antimicrobial

resistance. The scheduled trainings of the doctors is essential. This goes through the reinforcement of the training concerning the antibiotherapy and the infectious diseases and to make an appropriate diagnosis of bacterial infection of quality. It is important that the doctors and those already in activity be more informed of the consequences of their prescription in term of evolution of bacterial resistance if we don't want to talk about post-antibiotherapeutic era in few decades. However, this action is simple, hardly expensive and of fast implementation. Training concerning the prevention of antimicrobial resistance must be implemented imperatively as well as in the university than professional. The prevention is an essential slope intervening in the resolution of problems of public health.

Only the quarter of the doctors have prescribed bacteriologic analysis in front of infectious syndrome and less than the half of them got positive. The prescription of bacteriologic analysis is not in the habit of general practitioners in Toamasina even in the whole island unless they meet antimicrobial resistance problems.

Concerning the knowledge of MDR bacteria, our study showed that the MRSA are the most known and old multidrug-resistant bacteria by the doctors, it is probably because of that that the doctors know them more than the others. The general practitioner of less than 35 years seems to know the MDR bacteria better than those more than 55 years. Those results highlighted the differences between the initial training between those two generations. It has already been demonstrated several times that the intern and the young doctors were more aware of the antimicrobial resistance problem than the older, and that their prescriptions respected more the recommendations [25, 26, 27]. The implementation of help system to the decision such as protocols for the infection met most frequently and the provision of antibiotherapy guide allow to limit the errors of prescription and especially of spectrum, and thus to stop the development of resistances. However, some authors remarked that despite the implementation of local recommendations from the standards of the consensus, gaps of prescriptions are still encountered [28].

CONCLUSION

The pediatric infectious pathology in town is varied and polymorph. A precise infection duly diagnosed needs the prescription of an antibiotic treatment. Our study shows that the prescription is not justified in some cases and that the molecules chosen by the general practitioners do not correspond to the suspected pathology. It is suitable to reinforce the messages about the uselessness of antibiotics in some infections and to establish an ongoing medical training project concerning the diagnosis and the treatment which might help to improve the quality of prescription of antibiotics. It is registered in a rich context of actuality on the need of the implementation of a national program so as to improve the good use of antibiotics, especially in town, to limit the emergence of resisting bacteria, with the main goal to elaborate documents of references about the prescription of antibiotics. The antimicrobial resistance is a real

problem of public health but which still seems to be too abstract for the general practitioner in Toamasina.

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