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Antibiotic Therapy for Early Ages and Asthma Development in School Children

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Abstract--- *The objective of the research was to determine the association between the use of antibiotics in Early ages and the development of asthma at school age, this study is a retrospective observational descriptive approach with a quantitative case-control approach. Medical records of patients from the pediatric area of a Guayaquil hospital were reviewed. The total sample was 366 children. The cases (n = 183) were chosen from the hospital database of children between 5 and 12 years old who have been diagnosed with asthma. Controls were matched in equal numbers and proportions. 43% of the cases used antibiotic therapy before 5 years, with amoxicillin being the most beta-lactamase inhibitor, the most widely used antibiotic (28.8%). The most frequent comorbidity was acute upper respiratory infection (38%). Among the controls, the most used antibiotic corresponded to amoxicillin (34.8%), while the most frequent infection was the same as for the cases (50.0%). An analysis was performed to determine if the difference in distribution concerning the use of antibiotics is significant between cases and controls and it was determined that there is a much higher percentage of antibiotic use in cases than in controls (60.1% vs. 25.7% ; p = 0.011). The analysis reflects an association between the use of antibiotics at an early age and the appearance of asthma at school age. Thus, the use of antibiotics in children under 5 years increases the risk 4.5 times of having asthma at school age.*

Keywords--- *Antibiotics, Asthma, Children, Immune System, Intestinal Microbiome*.

I. INTRODUCTION

The overuse of antibiotics is a growing public health problem. While outpatient antibiotic prescriptions have decreased significantly in the past two decades, the use of broad-spectrum inpatient antibiotics has increased (Kuehn, 2014). To promote conservative administration of antibiotics in countries such as the United States, antibiotics remain the most frequently prescribed outpatient prescription medication and account for approximately 25% of all pediatric prescription prescriptions (Chai et al., 2012). Five of the six main medications prescribed for children in that country are antibiotics, with Amoxicillin and Azithromycin being the most common (Chai et al., 2012). A study investigating the bacterial prevalence and antibiotic prescription trends for acute pediatric respiratory tract infections estimated that around 30% of antibiotic prescriptions are unnecessary (Kronmanet al., 2014). Consequently, there are approximately 11.5 million antibiotics prescribed annually for diseases in which a bacterial pathogen is not the expected etiology of the disease (Kronman et al., 2014).

While antibiotics are an important part of modern medical care, there are some potential adverse effects to consider, including unwanted side effects, antibiotic resistance, and disruption of the gut microbiota (Ni et al.,

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2019). The gut microbiome hypothesis that has recently emerged as a link between antibiotic exposure and disease development is that the relationship between early antibiotic exposure and dysbiosis of the gut microbiota may have significant implications for children's health. now and as they grow into adults (Nyandra et al., 2018; Suryasa et al., 2020; Rusmini et al., 2018).

The gut microbiota is made up of billions of microbes in the intestinal tract and contains more than a thousand different species of bacteria (Bäckhed et al., 2015). Previous studies have suggested that the first year of life represents a critical period of development and that around three years of age, it is fully mature (Biedermann & Rogler, 2015).The gut microbiota has been shown to play an important role in the human immune system and the maintenance of homeostasis, alterations are an alleged mechanism underlying the "hygiene hypothesis", in which children who are exposed to a Wide Range of environmental and nutritional factors that promote a diverse and robust microbiota are less prone to atopy and asthma (Ege et al., 2011). Intestinal dysbiosis has been linked to early disruptions in the regulation of the immune system (Wu & Wu, 2012) and, therefore, to the development of chronic inflammatory and atopic respiratory diseases such as asthma and allergic rhinitis (Frati et al., 2018; Pascal et al., 2018).

There is evidence that suggests the existence of a connection between early exposure to antibiotics that alters the development of the intestinal microbiota and subsequently, the immune system, which increases the risk of developing the previously mentioned diseases (Nogacka, 2018; Sutapa et al., 2018; Keohin & Graw, 2017; Arini et al., 2019). However, relatively few studies have investigated the effects of timing of antibiotic exposure on future health outcomes, and whether there is a period during early development when the gut microbiota is most susceptible to gut dysbiosis. Furthermore, few studies have examined the relationship between increasing antibiotic doses and subsequent effects on the propensity to develop the disease in a dose-response relationship.

The present study aims to investigate this relationship, as well as the effects of early exposure to antibiotics and the future propensity to develop the disease later in childhood, through a retrospective study of asthmatic patients in the Pediatric Service of the Hospital del North of Guayaquil Los Ceibos. Consistent with the gut microbiome hypothesis, it is hypothesized that children exposed to antibiotics during the first years of life will be more likely to be diagnosed with allergic asthma at school age, compared to children who did not receive antibiotics during the same age.

II. MATERIAL AND METHOD

This is a descriptive retrospective observational study with a quantitative approach of cases and controls, carried out by reviewing the medical records of patients in the pediatric area of the Hospital del Norte de Guayaquil Los Ceibos. The variables used were: age, sex, asthma, the disease that justifies the use of antibiotics, use of antibiotics, the family of the antibiotic, complete treatment of the infection, age of antibiotic use.

The universe of this research is made up of all the patients between 6 and 12 years old treated in the pediatric area of the General Hospital of the North of Guayaquil Los Ceibos. A sample made up of cases and controls was selected from the study population. Their selection was defined according to the inclusion and exclusion criteria

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described below: asthma diagnosis according to the ICD-10 code J450 and J45 of the outpatient hospital; control patients with ICD-10 code A010-Z988; the record of the constancy of antibiotic use in patients from 0 to 5 years of age.

The analysis of the clinical characteristics based on the variables was obtained from the medical records. The qualitative variables were expressed in frequencies and percentages, and measures of central tendency and dispersion (Mean and SD) were also applied for the quantitative variables. Comparison of proportions between groups was carried out using the McNemar test averages were compared Quantitative using the Wilcoxon test or T-test for paired samples, according to the number of groups in which the averages are to be compared, considering a value of $p < 0.05$ as statistically significant. A contingency table with Fisher's exact test and finding an Odd ratio etiological relationship will be used to assess the existence of an association between the use of antibiotics and the pediatric patient population of the General Hospital of the North of Guayaquil Los Ceibos.

III. Analysis and Discussion

This research was designed as a case-control study. The 183 cases considered in the present study were chosen from the database of children diagnosed with asthma, based on the ICD-10 code of the clinical history and treated in the pediatric area of the Hospital General del Norte de Guayaquil Los Ceibos, in the period 2018. The age of the children included in this study was limited to an age range of 6 to 12 years.

The corresponding controls (n = 183) were selected from among the patients from the same database who were treated for a cause other than asthma and any respiratory symptoms under the ICD-10 classification, to minimize the risk of bias. of selection. Cases and controls were matched in 1: 1 ratio by age (± 2) and sex. The McNemar test was used to assess the association between antibiotic exposure and asthma risk in a univariate way. Unadjusted models were adjusted to obtain the odds ratios (Odd Ratios), with 95% confidence intervals. Version 24 of the software was used *SPSS* for data analysis, from which tables and graphs were generated. A $p < 0.05$ value was defined as a significant result for all analyzes.

Demographic Characteristics and Use of Antibiotics in Cases and Controls

Because a great variability was found in the age range and to avoid bias in the study, the age difference between cases and control was calculated using 1: 1 ratio pairing per age (± 2) and sex.

Regarding the epidemiological characteristics of the study subjects, of the total study sample, 231 corresponded to male patients and 135 were female, which corresponds to 63.1% and 36.9% respectively. Of the total of patients, 187 were between 6 to 8 years old, 80 were between 9 to 10 years old and 89 were between 11 to 12 years old.

A table with the main characteristics of the sample is presented below. Regarding the age of the sample, 98 of the patients included in the study area in the age range of 6 to 8 years, which corresponds to 53.6%, being the majority. To avoid bias in the study, the age difference between the cases and controls was ±2 years, which was calculated using the statistical program *MedCalc*. Next, Table 1 shows the demographic characteristics of the sample studied.

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Table 1: Demographic Characteristics of the Total Sample, Cases, and Controls

Main characteristics		Total (%)	Cases (%)	Controls (%)
Sex	Female	135 (36.9)	67 (36.6)	68 (37.2)
	Male	231 (63.1)	116 (63.4)	115 (62 , 8)
Age categories	6 to 8 years	187 (53.8)	99 (54.1)	98 (53.6)
	9 to 10 years	80 (21.9)	44 (24)	36 (19.7)
	11 to 12 years	89 (24.3)	40 (21.9)	49 (26.8)

Figure 1 describes the distribution of antibiotic use of the sample studied. 43% of patients reported having used antibiotic therapy before 5 years.

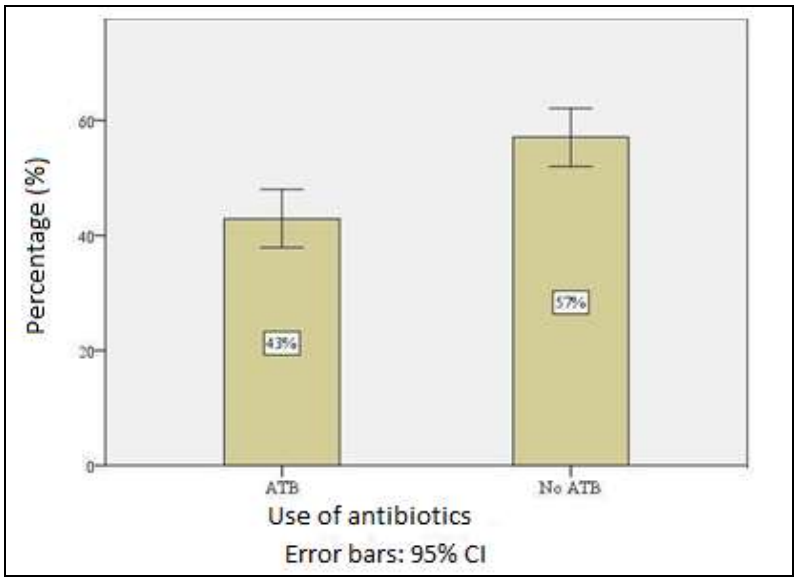

Figure 1: Distribution of Antibiotic Exposure in the Study Case Population

Of all the cases analyzed in this study, 43% had exposure to different antibiotics at ages less than five years. Of 183 cases, 118 used antibiotic treatments, of which Amoxicillin + IBL (Clavulanic acid) was the most frequently supplied (28.8%), followed by Metronidazole and second-generation Cephalosporin in 13.6%, and 12, 7% respectively, as shown in Table 2.

Table 2: Frequency and Percentage of Antibiotics used by Patients with Asthma (Cases)

Antibiotic	Frequency	Percentage
Albendazole	11	9.3
Amoxicillin	4	3.4
Amoxicillin + IBL	34	28.8
Ampicillin	1	0.8
Ampicillin + Sulbactam	4	3.4
2nd Generation Cephalosporin	15	12.7
Ceftriaxone	1	0.8
Cotrimoxazole	8	6.8
Dicloxacillin	3	2.5
Gentamicin	1	0.8
Macrolides	11	9.3
Metronidazole	16	13.6
Metronidazole + Albendazole	7	5.9
Nitazoxanide	1	0.8
Penicillin	1	0.8

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Recent studies suggest an association between increased allergic disease and early alterations of the intestinal microbiome. Ni et al. (2019) carried out a retrospective review of existing files at Epic of Loyola University Medical Center (LUMC) between the years 2007 to 2016. The study included 7 224 children from 1 to 10 years old, who belonged to different services: hospitalized, emergency room, immediate attention and outpatient consultations in the institution. The researchers demonstrated that antibiotic administration during the first 12 months of life was significantly associated with lifetime asthma (OR = 2.66; C. I 1.11–6.40) but not with allergic rhinitis. The results also indicated a significant association between the use of antibiotics with asthma (OR = 3.54; C. I 1.99–6.30) and allergic rhinitis (OR = 2.43; C. I 1.43–4.11) (Ni et al., 2019). In the reviewed reports, children received at least one of the following antibiotics in this study: penicillin, amoxicillin, gentamicin, vancomycin, clindamycin, sulfamethoxazole/trimethoprim, cephalexin, ampicillin, cefotaxime, ceftriaxone, azithromycin, and ceftazidime (Ni et al., 2019). The antibiotics used are similar to the antibiotics included in the therapy of the patients in the present study, which were the most widely used. 28.8% of asthmatic patients (cases) in the present study also used amoxicillin plus a beta-lactamase inhibitor, and 12.7% used second-generation cephalosporin. These results provide support for a conservative approach to antibiotic use in early childhood.

Distribution of Comorbidities Justified Exposure to Antibiotics in Study Case Population

Among the 183 selected cases, 121 comorbidities were identified, among which the most prevalent was acute upper respiratory infection (38%), followed by intestinal parasitosis (30.6%) and lower respiratory tract infections (11.6%), as can be seen in Figure 2. There is coherence between comorbidity and the antibiotic plan used.

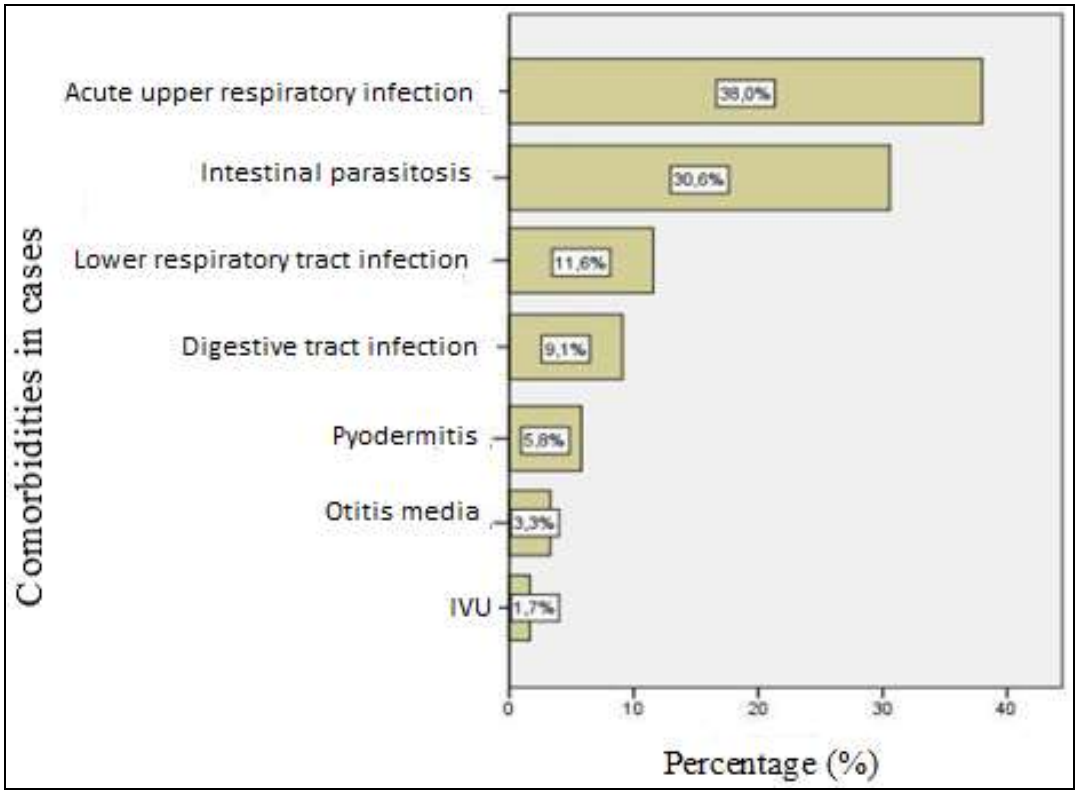

Figure 2: Percentage of Causes for ATB Use in Asthma Patients (Cases)

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Exposure to antibiotics of the control population

As detailed in Table 3 and Figure 3, 46 controls used some antibiotics, with Amoxicillin being the most frequently used drug (34.8%), followed by Metronidazole and Cephalosporins in the same number and percentage (17.4%).

Table 3: Frequency and Percentage of Antibiotics Used by Controls

Antibiotic	Frequency	Percentage
Amikacin	1	2.2
Amoxicillin	16	34.8
Ampicillin	5	10.9
Cephalosporin	8	17.4
Cotrimoxazole	2	4.3
Dicloxacillin	1	2.2
Macrolides	5	10.9
Metronidazole	8	17.4

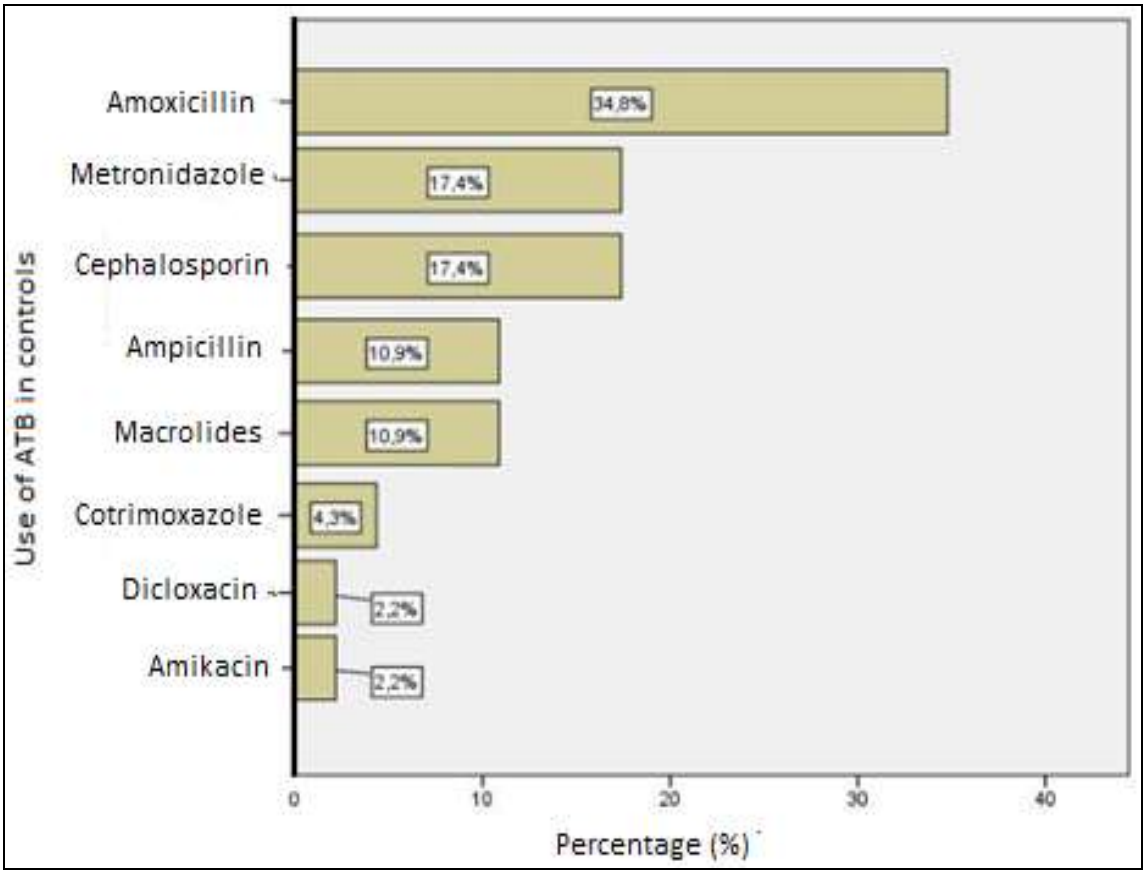

Figure 3: Percentage of Antibiotics Used by the Controls.

Table 4 and Figure 4 describe the comorbidities that justified the use of antibiotic therapy in the controls, of which 23 presented acute upper respiratory infection, which represented 50% of the total, followed by intestinal parasitosis and infection of the lower respiratory tract, with 17.4% and 15.2% respectively. This is related to antibiotic therapy and disease and treatment are coherent.

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Table 4: Frequency and Percentage of the Pathologies for which ATB was Prescribed in the Controls

Causes of ATB use	Frequency (N = 46)	Percentage (%)
Acute infection of the upper respiratory tract	23	50.0
Infection of the lower respiratory tract	7	15.2
Infection of the digestive tract	5	10.9
IVU	1	2.2
Otitis media	1	2.2
Intestinal parasitosis	8	17.4
Pyodermitis	1	2.2

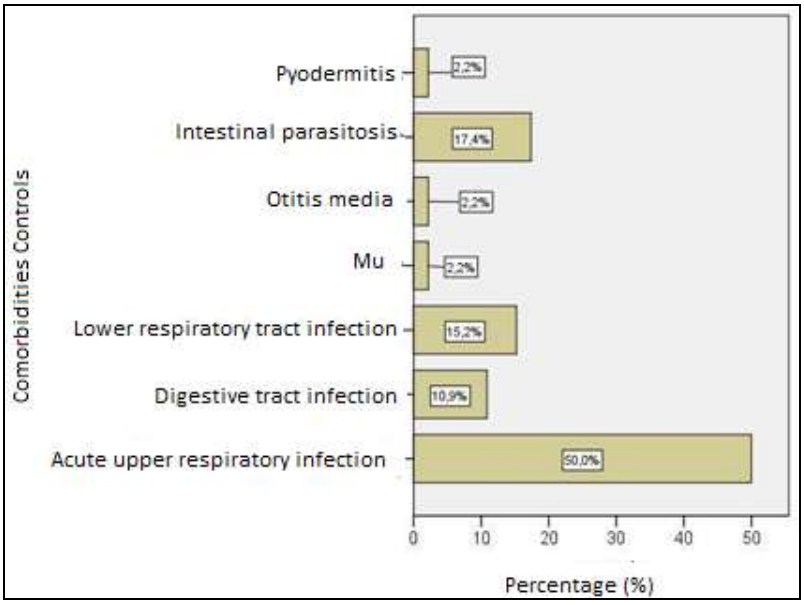

Figure 4: Frequency of causes for the use of ATB in controls

Figure 5 describes the difference between the average duration of antibiotic therapy in the cases. The average duration was 5.9 and 5.3 days in cases and controls, respectively.

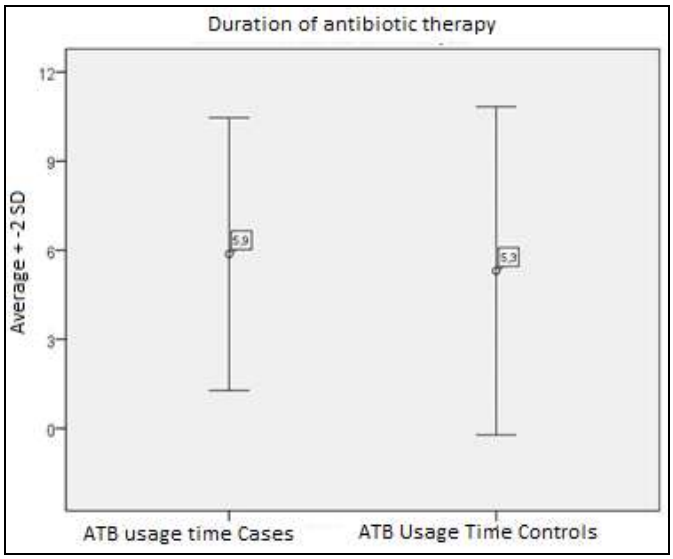

Figure 5: The Difference Average Duration of Antibiotic Therapy (days) in Cases and Controls

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Figure 6 shows the difference between the average age of cases and controls in which antibiotic therapy was administered for the first time. It is evident that both averages are very similar, being 2.85 and 2.72 for cases and controls, respectively, which shows that age during the use of antibiotics does not act as a confounding factor since both groups are similar in this regard.

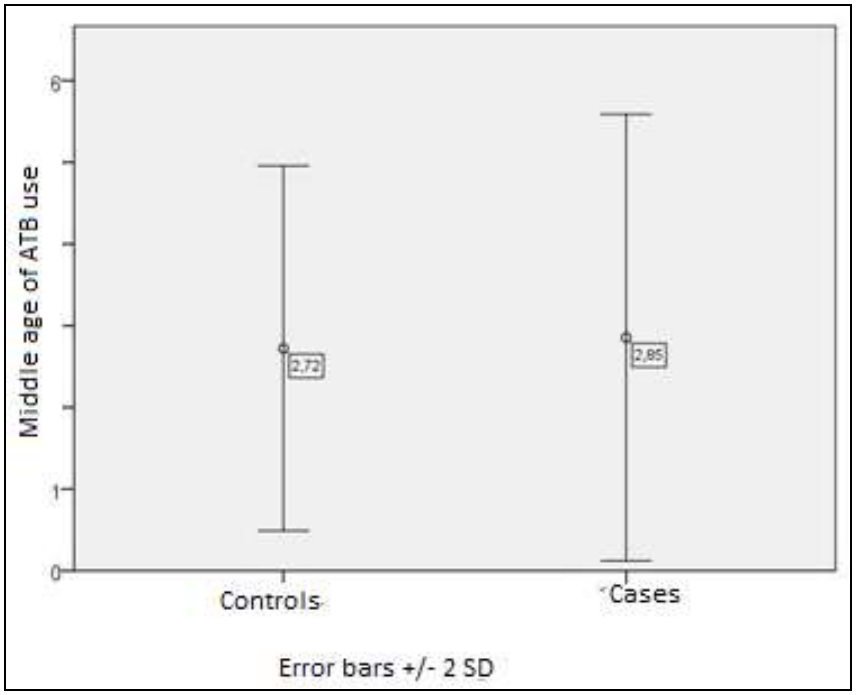

Figure 6: Difference between the Average Age (years) at which Antibiotic Therapy was Administered in Cases and Controls for the First Time

Relationship of Antibiotic Exposure Early Age and Asthma Development of Children

Table 5 indicates that the *OR* is 4.5, with a 95% confidence interval, ranging from 2.7 to 7.5, with a *p-value of* less than 0.001. These results demonstrate that the population of children under five years of age who received antibiotic treatments has 4.5 times the risk of developing asthma at school age.

Table 5: Contingency Table: Difference in Distributions of the Use of Antibiotics

ATB use	Cases (%)	Controls (%)	OR (p-value)
Yes	110 (60.1)	47 (25.7)	4.5 (0.001)
No	73 (39.9)	136 (74.3)	

Table 6 shows the results of the applied test. The variables sex and age were used because they are determining factors. “NS” was added, given the existence of significance, since both groups are equal. As can be seen, 60.1% of cases and 25.7% of controls used antibiotic therapy. The p-value used was 0.011, which is highly significant, that is, there is a univariate association. An association is observed between the use of antibiotics at an early age and predisposition to develop asthma at later ages. An analysis was performed to determine if the difference in distribution concerning the use of antibiotics is significant between cases and controls and it was determined that there is greater use of antibiotics in the cases than in the controls (60.1% vs. 25.7 %; p = 0.011).

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Table 6: Distribution of Demographic Characteristics and the Use of Antibiotics in the Sample Studied

Variables		Cases (n = 183)	Controls (n = 183)	P value
Antibiotic use, n (%)		110 (60.1)	47 (25.7)	0.011
Sex, n (%)	Female	67 (36.6)	67 (36.6)	NS
	Male	116 (63.4)	116 (63.4)	NS
Age, mean ± SD		8 ± 2	9 ± 2	NS

The results are consistent with several investigations carried out in various hospital institutions in different parts of the world. In this way, similarities are observed in the results obtained by Hoskin-Parr et al. (2013), who described the association of the use of antibiotics in childhood and the alteration of the intestinal microflora during a critical period for immune development. The study involved 4 952 children aged 0 to 2 years and the development of asthma, eczema or hay fever at 7.5 years of age was assessed in a longitudinal birth cohort (Hein, 2019). It was shown that the patients complied with antibiotic treatment during childhood (0–2 years), which showed that they were more likely to have asthma at 7.5 years (OR 1.75, 95% CI 1.40 –2.17), and the probabilities (OR [95% CI]) increased with the greater number of consumption of this type of substance: once 1.11 [0.84–1.48]; twice 1.50 [1.14–1.98]; three times 1.79 [1.34–2.40]; four times or more 2.82 [2.19–3.63] (Hein, 2019). Their results indicated a robust and dose-dependent association between the use of antibiotics in the first 2 years of life and asthma at 7.5 years (Hein, 2019; Adhi et al., 2018; Tjiang & Sidiartha, 2018; Leyva et al., 2018). Therefore, it was suggested that the effect appears to be associated with a cumulative period of exposure, contrary to what was thought to be related to a critical period during the first two years of life.

It also agrees with Miter et al. (2018), whose study aimed to determine if there is an association between the use of antibiotics or acid suppressant drugs in the first 6 months of childhood and the development of allergic diseases in early childhood. The study was a retrospective type of cohort in 792,130 children who were beneficiaries of the Department of Defense's TRICARE, with a medical birth record in the database of the Military Health System between October 1, 2001, and September 30. of 2013. The researchers found that of the 792,130 boys (395,215 [49.9%] girls) included in the analysis, 131,708 (16.6%) were prescribed an antibiotic during the first 6 months of life, and obtained as a result, there is an adjusted risk ratio of 1.41 (95% CI, 1.31-1.52) for asthma if prescribed in children younger than 6 months of age. This study found associations between the use of antibiotic medications during the first 6 months of childhood and the subsequent development of allergic disease (Miter et al., 2018). This result demonstrates that antibiotics should be used during childhood only in situations of clear clinical benefit, since early exposure to drugs that can alter the microbiome, including antibiotics and acid-suppressing drugs, can influence the probability of allergy. The OR value in Table 7 demonstrates the number of times asthma risk increases using antibiotics before 5 years of age.

Table 7: Unadjusted Binomial Conditional Regression Showing the OR of Antibiotic Use as a Predictor of Asthma

Variables		OR crude (95% CI)	p value
Antibiotic use	No *	1.00	
	Yes	4.5 (2.7 - 7.5)	<0.001

Metzler et al. (2019), carried out a study which included a total of 1,080 children belonging to a European birth cohort (PASTURE). Data collected on antibiotic exposure during pregnancy and/or the first year of life and allergic

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diseases were collected using questionnaires from pregnancy to 6 years of age and analyzed using logistic regression. They demonstrated that antibiotic exposure in utero was significantly and positively associated with atopic dermatitis and food allergy (Metzler et al., 2019). The strongest effect was on diseases that started in the first year of life (for atopic dermatitis: OR 1.66, 95% CI 1.11-2.48 and for food allergy: aOR 3.01, 95% CI 1, 22-7,47 Antibiotics in the first year of life were positively associated with atopic dermatitis up to 4 years (aOR 2.73, 95% CI 1.66-4.49) and also suggested a dose-relationship the response, as well as a trend with asthma between 3 and 6 years (aOR 1.65, 95% CI 0.95-2.86), was observed.(Metzler et al., 2019)previous findings show positive associations between antibiotic exposure and allergies, especially atopic dermatitis and food allergy during the first year of life, after prenatal exposure, and atopic dermatitis and after asthma postnatal exposure to antibiotics in infants born in rural environments. Figure 7 shows the percentage of use of antibiotics in cases and controls without asthma.

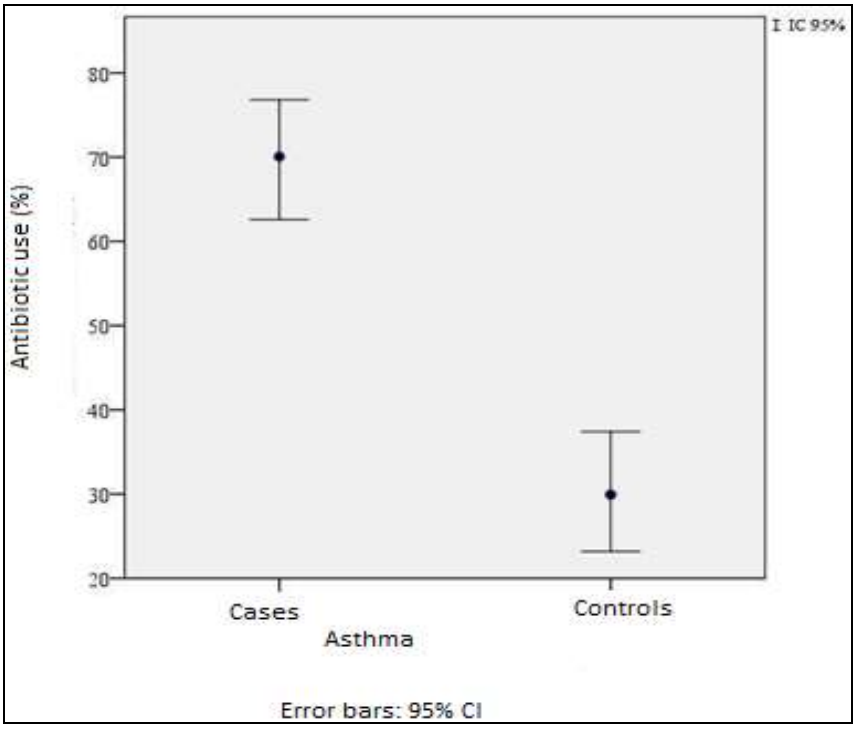

Figure 7: Percentage of Antibiotic Use in Asthma Patients (Cases and Controls)

Antibiotics kill not only pathogenic microorganisms, but they can also kill beneficial microorganisms, thereby affecting the native microbiome. Physiologically, the human mucosa has a large number of harmless commensal organisms, and this respiratory symbiosis is vital to the normal function of the respiratory tract. Any change in the mucosal immune system could lead to changes in the composition of symbiotic bacteria, which in turn can affect the response of the mucosal immune system to other immune stimuli. Therefore, multiple uses of antibiotics could increase the risk of immune dysfunction and allergic diseases. Evidence of this is the study published by Cole-Johnson (Hein, 2019; Giler et al., 2019; Sumba et al., 2020), of the Henry Ford Health System in Detroit. He reported at the 2019 American Thoracic Society (ATS) International conference in Dallas, that disruption of very early gut microbial communities impact the outcome of asthma at ages 10 and 11. As well as the chances that a 10-year-old boy has allergic asthma increases if he was born by emergency cesarean section, does not have a dog, is

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black and has an immature intestinal bacterial community (Miter et al., 2018; Novayanti et al., 2018; Wiardani et al., 2018; Markolinda & Sawirman, 2018). In this sense, doctors must be rigorous when prescribing antibiotics to neonates and children, it is necessary to determine if the antimicrobial drug is necessary or if there is an alternative treatment that can be tested.

The results observed in this study and those obtained in various investigations suggest that the use of antibiotics in the first years of life is associated with an increased risk of developing the allergic disease in late childhood, increasing the risk of allergic rhinitis, asthma and common allergic diseases in late childhood (Wang et al., 2013; Rodriguez et al., 2018; Praharsini et al., 2018; Sidiartha & Pratiwi, 2018).

IV. CONCLUSION

The total population was 366 patients, 183 school patients attended with a diagnosis of asthma and 183 patients with other diseases who needed to use antibiotics due to their comorbidities were identified at the Hospital General del Norte de Guayaquil Los Ceibos in 2018. From a total of patients, 231 correspond to male patients and 135 to the female sex, which corresponds to 63.1% and 36.9% respectively. Of the total of patients, 187 were between 6 to 8 years old, 80 were between 9 to 10 years old and 89 were between 11 to 12 years old.

Of all patients, 43% used antibiotic therapy between 0 and 5 years. Among the cases, the most widely used antibiotic was amoxicillin + IBL (clavulanic acid), supplied more frequently (28.8%), followed by metronidazole (13.6%), followed by second-generation cephalosporin (12.7%). Among the most prevalent comorbidities in the cases was acute upper respiratory infection (38%), followed by intestinal parasitosis (30.6%) and lower respiratory tract infections (11.6%). Among the controls, amoxicillin was the most frequently used (34.8%), followed by metronidazole and cephalosporins in the same number and percentage (17.4%). Concerning comorbidities, acute upper respiratory infection appears as more frequent (50%), followed by intestinal parasitosis and lower respiratory tract infection, with 17.4% and 15.2%, respectively.

The duration of the antibiotic therapy was 5.9 days in the cases and the controls, it was 5.3 days. The difference in age averages of the use of antibiotics for the first time, both in controls and in cases, were very similar, being 2.72 for controls and 2.85 for cases. This study has shown that the use of antibiotics at an early age is related to the appearance of asthma at school age in the study population. The use of antibiotics at ages less than five years increases the risk of developing asthma in school-aged children by 4.5. This could be explained by the increased susceptibility of the immune system at that age.Antibiotics are important medications to treat bacterial infections, prevent the spread of the disease, and reduce serious complications of the disease. However, overuse and misuse of antibiotics are key factors contributing to antibiotic resistance, which is one of the most serious public health threats today.

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