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Bioestadística y epidemiología: una mirada a los roles en la investigación

Biostatistics and epidemiology: a look at roles in research

Mr. Editor:

Current science, in its vertiginous advance, increasingly requires individuals to train and specialize in topics that allow them to make robust proposals for solutions to health problems. In my experience working as a statistical data analyst in joint work with groups of health professionals, I have observed that, for most researchers it is very difficult to recognize the difference between a statistician dedicated to working with problems that include measurements in living beings (in this case human individuals) which is generally called biostatistics (1) and a professional who is concerned with the study of the causes, the risks, the dispersion of diseases and health problems, which is called an epidemiologist (1,2).

In a world where interdisciplinarity and teamwork is increasingly necessary, especially in medical research, I consider important to identify the role of each member of the work team because this allows to give the value that the activities carried out deserve. From my perception, the epidemiologist makes a very important contribution in the identification of the health problem that needs to be studied and which dynamics need to be understood. In the hands of these professionals, it is to establish the best approximation strategy (study design) to address the issue, identify the factors that should be controlled and how they should be controlled; participate in the construction of measurement protocols and the definition of events of interest (outcomes) among other important methodological aspects. For his part, the biostatistician, must understand the problem from a holistic and systemic vision of it, participates in the construction of the information system and perhaps his most important task is to obtain the quantitative results of the project from mathematical procedures applied to the data collected in the field by the other professionals of the group (including the epidemiologist). So, it is easy to see that the two professionals despite keeping similarities in some of their tasks, have well-defined roles within the project.

Generally, public health schools and health schools that offer graduate degrees in epidemiology consider two, three, and up to four statistics courses in their curriculum, in which students learn some basic concepts of probability and statistics and emphasize the use of already established statistical methods that must be used, assuming that the study design meets a certain number of theoretical assumptions. Nevertheless, for the biostatistician, it is clear that, although the strategies developed to obtain the data in the field are as rigorous as possible, there will always be aspects that cannot be controlled or that are not easily manipulated (such as the willingness of the subjects to participate, to cite a simple aspect), which implies that, the data collected in the field, not necessarily meet all the requirements imposed by the theoretical assumptions, an aspect that was reported since the third decade of the last century (1,3,4). These situations, which may be common in the practice of health research, induce to rethink and evaluate in the light of reality and context, how to develop statistical methodologies by making modifications to existing methods or creating new ones that allow a more robust or realistic approach to the problem under study, work that can be done by the biostatistician with the support not only of the epidemiologist but of all professionals of the research team (4).

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Prevalencia de sobrepeso en los pacientes pediátricos con colelitiasis, atendidos en el Hospital San Rafael de Tunja durante los años 2010-2019

Prevalence of obesity and cholelithiasis in pediatric patients of San Rafael hospital de Tunja during the years 2010-2019

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Abstract

Objective: To determine the prevalence of overweight in pediatric patients with cholelithiasis treated at the San Rafael de Tunja hospital during the years 2010 - 2019.

Materials and methods: This is an observational, descriptive, cross-sectional, and retrospective study, in which the characteristics of cholelithiasis were evaluated in patients under 18 years of age. Sociodemographic, clinical, imaging, and therapeutic variables were evaluated.

Results: 84 clinical records of patients diagnosed with cholelithiasis were reviewed in a period between 2010 to 2019. A percentage of 69.1% were female and 30.9% were male. The average age of the patients was 15.07 years, the prevalence of overweight was 35.7%, and 21.4% was obesity. The most frequent manifestations were nausea (85.71%), vomiting (84.52%),

and Murphy's sign positive (83.33%). In 76% of the patients, the gallstones were unique since these had an average size of 7.45 mm (with a minimum of 1 mm and a maximum of 25 mm). 26.1% of the patients received conservative treatment while 73.8% of them were treated by surgery. From these, 50% of the cases were treated by open surgery and the rest by laparoscopic procedure, of which 2.43% required intraoperative conversion. Finally, the most common complications presented were liver abscess in 2.38% and pancreatitis in 4.76% of the patients.

Conclusions: More than the half of children with cholelithiasis were obese (21.4%) and overweight (35.7%), which indicates a public health problem since it may affect other pathologies in the future, in addition to being a strong predictor of the pathology under study in this article.

Keywords: Obesity, cholelithiasis, risk factors.

Introduction

In the pediatric population 20 years ago, cholelithiasis was considered an uncommon diagnosis and was generally associated with hematological diseases such as sickle cell disease, hereditary spherocytosis, hemolytic anemia, and thalassemia major (1,2).

The exact prevalence of gallstones worldwide in pediatric patients is variable, in Europe it was estimated that the overall prevalence of cholelithiasis in pediatric patients was 0.13-2%, while in Japan the approximate prevalence is less than 0.13% (3). Currently, the number of reported cases has increased, it is associated with the increase in the use of ultrasound in unexplained abdominal pain and with the exponential increase in childhood obesity (4).

In Latin America the obesity rate is among the highest in the world, one in 5 children under 20 years of age is overweight or obese, in turn, the incidence of comorbidities associated with obesity in this population has increased (5). Latin America shows an upward pattern in terms of overweight figures according to surveys in 2015 compared to those of 2010. The prevalence in Colombia, although it is one of the lowest in Latin Amer-

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ica, showed an increase of 1.4% from 4.9% to 6.3% of the population with this condition (6).

According to a study published in 2014, it is estimated that 21.8% of the population living in Tunja suffers from some type of overweight, this was mainly associated with the intake of hypercaloric foods and the low consumption of healthy foods (7). In the National Survey of Nutritional Situation (ENSIN for its acronym in Spanish) carried out in 2015 for the pediatric population, figures of overweight were evidenced in up to 6.3% in children aged 0 and 4 years, 24.4% in children aged 5-12 years and 17.9% in children aged 13 and 17 years (5).

In Colombia and the Boyacá department the search for studies of cholelithiasis in pediatric patients was unsuccessful, currently there are no population studies of this pathology. Therefore, the objective of the research is to determine the prevalence of overweight in pediatric patients with cholelithiasis treated at the San Rafael hospital of Tunja during the years 2010-2019.

Materials and methods

An observational, descriptive, cross-sectional, and retrospective study was conducted. The research was carried out at the San Rafael University Hospital of Tunja, located in the Boyacá department, where the review of medical records of pediatric patients under 18 years of age treated between 2010 and 2019 was carried out.

No sample size was estimated, as all patients who met selection criteria were included. Among the inclusion criteria, patients under 18 years of age with the diagnosis of cholelithiasis identified with the ICD codes 10 (K800 to K808), attended between the period from 2010 to 2019 and who had complete information on the chosen variables were considered, while those with incomplete information (by referral to another institution or by admission with extra-institutional surgery) were excluded).

The variables that were included were: age, origin, gender, history such as diabetes mellitus, arterial hypertension, kidney disease, use of psychoactive substances (PS), familial biliary lithiasis, parenteral feeding, hospitalizations in ICU, use of oral contraceptives, pregnancies, hemolytic anemia, body mass index (evaluating the presence of obesity based on growth and development curves), predominant symptoms, histopathological findings, paraclinical, imaging, treatment, time of hospital stay and complications.

The data were collected by two researchers between November the 4th

and the 18th, 2019, using a collection sheet. The database was registered in Excel version 2013 and analyzed in the statistical package SPSS version 21. The univariate analysis was performed by a descriptive statistic to the selected population, it determined absolute and relative frequencies in the categorical variables, with the quantitative variables measures of central tendency (mean, median) and dispersion measures (standard deviation and interquartile range) were calculated according to the variable distribution.

Ethical considerations: Based on resolution 8430 of 1993, where "the rules for health research are established", in accordance with the previous regulations the proposed study is classified as a risk-free investigation.

Results

1. Sociodemographic characteristics

84 patients were included, of whom 69.1% were female and 30.9% were male. The average age of the patients was 15.07 years (SD ± 2.03) years, with an average body mass index of 24.6 cms/kg2 with (SD ± 4.13) cms/kg 2, and the time of evolution between the onset of symptoms had an average of 95.3 hours (minimum of 2 hours and maximum of 360 h).

In the population studied, 42.8% had normal BMI, 35.7% were overweight and 21.4% were obese. Regarding the place of residence, the urban area had a prevalence of 61.9% with respect to the rural area, which was 38.09% of the total number of patients. The comorbidities presented by the patients in order of frequency were family history 34.52%, use of hormonal birth control 7.14% (Monthly 5.95%, three- monthly 1.19%), recent pregnancy 5.95%, hypertension 2.38%, chronic kidney disease 2.38%, hemolytic anemia 2.38% and diabetes 1.19%. (Table 1).

«In Colombia and the Boyacá department the search for studies of cholelithiasis in pediatric patients was unsuccessful, currently there are no population studies of this pathology.

Table 1. Sociodemographic Variables

Sociodemographic characteristics	Normal weight (n:36)	Overweight (n: 30)	Obesity (n: 18)	Total (n:84)	CI 95%
Sex					
Female	22	20	16	58 (%)	59.16 - 78.93
Male	14	10	2	26	21.07 - 40.84
Age Groups					
7 to 9 years old	1	1	0	2	0.0 - 5.64
10 to 12 years old	6	2	0	8	3.24 - 15.8
13 to 15 years	11	11	9	31	26.59 - 47.22
16 to 17 years old	18	16	9	43	40.5 - 61.88
Residence					
Rural	18	10	4	32	27.71- 48.48
Urban	18	20	14	52	51.52 - 72.29
Comorbidities					
Diabetes	0	1	0	1	0.0 - 3.51
Hypertension	1	1	0	2	0.0 - 5.64
Chronic kidney disease	1	1	0	2	0.0 - 5.64
Family history	13	12	4	29	24.36 - 44.69
Use of hormonal birth control	2	4	0	6	1.63 - 12.65
Monthly	2	3	0	5	0.89 - 11.01
Three- monthly	0	1	0	1	0.0 - 3.51
Recent pregnancy	1	2	2	5	0.89 - 11.01
Hemolytic anemia	0	2	0	2	0.0 - 5.64

2. Clinical and paraclinical characteristics

The evolution time presented by the patients had an average of 95.3 hours (minimum of 2 hours and maximum of 360 hours). Among the clinical manifestations that occurred the most were nausea 85.71%, vomiting 84.52%, positive Murphy's sign 83.33%, abdominal pain in the right hypochondrium 73.80% and to a lesser extent dyspepsia 25%, generalized abdominal pain 25%, jaundice 20.23%, fever 8.33% and dehydration 8.33%.

The average value of the paraclinical were: Leukocytes 12791.6/mm3 (SD ± 17732.1/mm3), Neutrophils 69.7% (SD ± 13.8%), lymphocytes 19.0% (SD ± 12.3%), platelets 310707.4/µL (SD ± 103381.9 /mcL), hemoglobin 14.3 g/dL (SD ± 1.67 g/dL), direct bilirubin 4.44 mg/dL (SD ± 25.95 mg/dL), indirect bilirubin 0.87 mg/dL (SD ± 1.35 mg/dL), aspartate aminotransferase (AST/GOT): 86.01 U/L (SD ± 110.12 U/L), alanine aminotransferase (ALT/GTP): 146.4 U/L (SD ± 215.09 U/L), creatinine 1.04 mg/dL (SD ± 2.87 mg/Dl), amylase 294.3 U/L (SD ±769.2 U/L), alkaline phosphatase (AP) 331.6 UIL (SD ± 618.5 UIL).

Regarding the ultrasound findings, it was found: the size of the calculations had an average diameter of 7.45 mm (minimum of 1.0 mm and maximum of 25.0 mm), were unique 19.04% and multiple 60.71%; the location of these was in gallbladder 96.42% and bile duct 2.38%; the gallbladder wall was thin 53.57%, thickened 11.90%, scleroatrophic 1.19%, and normal 33.33%; the liver was normal 89.28%, had hepatic steatosis 8.33% and hepatomegaly 3.57%; Normal bile duct 2.38% and dilated 19.04%; and the normal intrahepatic bile duct 21.42% and dilated 3.57% (Table 2).

Table 2. Clinical characteristics

Clinical characteristics	Normal weight (n:36)	Overweight (n: 30)	Obesity (n: 18)	Total (n:84)	CI 95%
Clinical chart					
Generalized abdominal pain	10	6	5	21	15.74 - 34.26
Abdominal pain in the right hypochondrium	26	23	13	62	64.41 - 83.21
Nausea	35	24	13	72	78.23 - 93.2
Vomiting	29	27	15	71	76.79 - 92.26
Fiver	3	3	1	7	2.42 - 14.24
Murphy's sign	28	28	14	70	75.36 - 91.3
Jaundice	4	10	3	17	11.65 - 28.83
Dyspepsia	11	7	3	21	15.74 - 34.26
Dehydration	5	2	0	7	2.42 - 14.24
Stones					
Multiple	27	26	14	51	50.27 - 71.16
Unique	8	4	4	16	10.65 - 27.44
Location					
Gallbladder	36	29	16	81	92.46 - 100
Bile duct and gallbladder	0	1	2	2	0.0 - 5.64
Gallbladder wall thickness					
Thin	21	17	7	45	42.91 - 64.24
Thickened	2	6	2	10	4.98 - 18.83
Scleroatrophic	0	1	0	1	0.0 - 3.51
Normal	13	6	9	28	23.25 - 43.41
Liver					
Normal	34	27	14	75	82.67 - 95.9
Hepatic steatosis	1	3	3	7	2.42 - 14.24
Hepatomegaly	1	1	1	3	0.0 - 7.54
Bile duct					
Normal	30	25	13	2	0.0 - 5.64
Dilated	6	5	5	16	10.65 - 27.44
Intrahepatic bile duct					
Normal	33	30	18	18	12.65 - 30.2
Dilated	3	0	0	3	0.0 - 7.54

3. Therapeutic characteristics

Of all patients, 26.1% received conservative treatment, while 73.8% were treated by surgery; in these cases, 50% of the intervention was open and in the other 50% the intervention was laparoscopic of which 2.43% required intraoperative conversion. Regarding complications, 2.38% of patients developed liver abscess, 4.76 developed pancreatitis, 1.19% of patients developed fistula or biliary lesion and 2.38% of patients had cholangitis. (Table 3).

Table 3. Therapeutic characteristics

Therapeutic and prognostic characteristics	Normal weight (n:36)	Overweight (n: 30)	Obesity (n: 18)	Total (n:84)	IC 95%
Conservative	12	5	5	22	16.79 - 35.59
Surgery	24	25	13	62	64.41 - 83.21
Open	8	16	7	31	26.59 - 47.22
Laparoscopic	16	9	6	31	26.59 - 47.22
Histopathology					
Chronic cholecystitis lithiasis	21	14	8	43	40.5 - 61.88
Acute cholecystitis lithiasis	1	5	4	10	4.98 - 18.83
Scleroatrophic gallbladder	2	6	1	9	4.1 - 17.33
Complications					
Liver abscess	0	1	1	2	0.0 - 5.64
Pancreatitis	1	1	2	4	0.20 - 9.31
fistula or biliary lesion	0	1	0	1	0.0 - 3.51
Cholangitis	2	0	0	2	0.0 - 5.64

Discussion

The sociodemographic aspects of the sample are like those series presented in the literature, which indicate that there is a higher incidence of pathology in the female gender with 69.1% which shoes that this result agrees with worldwide studies, this suggest that biliary lithiasis is more frequently in females, 73% according to the study of Matuszczak et al. (8,9).

The average age of the patients was 15.07 years as well as a Latin American study where it is recorded that biliary lithiasis is more frequent in the age group between 11 and 15 years (10), unlike Asian and European studies where a higher prevalence of 5-14 years is mentioned with predominance at 10.5 years (11,12).

In terms of the place of residence, the urban area had a prevalence of 61.9% cholelithiasis which was higher than the rural area; according to the study by Briceño et al. in a report of risk factors of the child population, there is evidence of a higher prevalence of overweight, obesity and sedentary lifestyle in the urban population because of factors such as diet and unhealthy lifestyle habits (13.14) unlike studies carried out in Asia where there is a prevalence of almost 75% in the rural population (11).

Overweight (35.7%) and obesity (21.4%) together with family history (34.52%) were identified as the main risk factors for developing cholelithiasis in the child population, data that agree with studies carried out in Europe and America where obesity was identified as the main risk factor in more than 50%, family history also has a high proportion especially those of the first degree and hemolytic disorders (14,15).

Another variable studied were hormonal birth control (7.14%) and pregnancy (5.95%), which generate high estrogenic loads and facilitate the increase in cholesterol levels and the decrease in the production of bile salts (16).

Regarding clinical characteristics, a high prevalence of gastrointestinal symptoms such as nausea (85.71%) and vomiting (84.52%) and signs of abdominal distress such as Murphy's sign (83.3%) and abdominal pain in the right hypochondrium (73.8%) ware found, findings that differ significantly with the Iranian literature where a higher prevalence of abdominal pain is reported (67%), and to a lesser extent vomiting (35%) (17,18). However, this study agrees with the Indian literature where it is reported that 61.1% of patients presented symptoms among which pain in the right upper quadrant (51.4%) stands out as the main symptom, epigastralgia, nausea (33.8%) and vomiting (28.4%) (19.20). On the other hand, an Italian study reports symptoms only in 42.7% of patients (21). In Turkey, symptoms are also reported in 80.4% of patients, abdominal pain as the predominant symptom in 60% of patients, and vomiting only in 9.8% of patients (22).

In different published studies, it is described that the main alterations of the laboratory are observed in the hematic picture with leukocytosis, elevation of aminotransferases and total bilirubin (22,23), results that correlate with the findings obtained in this study where the main alterations were observed in the hematic picture with leukocytosis (12,791), elevation of AST (86.0119), ALT (146.4) and bilirubinemia (4.4), by being these markers indicators of worsening of the clinical picture (cholecystitis, migration of

calculus to bile duct, sepsis, pancreatitis) but not definitive diagnoses of the disease (24).

It was found in this study that of the 84 medical records reviewed, 19.04% presented unique stones, unlike Soto et al. who reports that of the 181 patients analyzed, 54.9% of these had single stones (13); it was also found that 60.71% of the stones found by ultrasound were multiple unlike Espigares et al. that in his study he found that only 26% of the 50 patients reviewed had multiple stones, likewise 4.38% of stones in the bile duct were presented and Espigares reported a total of 7.8% (25).

Of the total number of patients, 26.1% received conservative treatment through observation and intervention in unhealthy lifestyles, while 73.8% were treated by surgery (50% laparoscopically and 50% open intervention), a result that contrasts with a study published by an Iranian journal where conservative treatment with ursodeoxycholic acid was used in asymptomatic patients (18); according to research by Rossi et al. surgical management is discussed in cases of typical bilateral symptoms, evidence of black pigment stones and conservative in cases of nonspecific symptoms (26).

In a report by Walker et al. the number of cholecystectomies performed on children increased by 213% over a nine-year period, until 2012. In addition, the incidence of cholecystectomy in England has tripled since 1997 in the pediatric population. Obesity is a frequent risk factor associated with the formation of cholesterol gallstones in the pediatric population, increasing almost 3 times the probability of developing gallstones compared to a person with a normal weight (1).

The main complication found was pancreatitis in 4.76% followed by cholangitis and liver abscess 2%, these results correlate with a study conducted in Latin America and Europe that indicates as the main complication pancreatitis followed in a lower proportion of cholelithiasis and calculous cholecystitis.

The present study shows a public health problem, since in the past obesity and overweight had a low frequency, affecting mostly the adult population; however, nowadays and even knowing all the risks that can generate

«In addition, the incidence of cholecystectomy in England has tripled since 1997 in the pediatric population. Obesity is a frequent risk factor associated with the formation of cholesterol gallstones ...

in the long term, its prevalence has increased affecting all age groups, which is why it has been known as the epidemic of the twenty-first century (27). It has been found that obesity is not only associated with pathologies such as the one analyzed in the present research (cholelithiasis), but it has also been found that long-term obese children and adolescents have an increased risk of presenting metabolic syndrome, mellitus diabetes, cardiovascular diseases, cancer, asthma, and deaths before 50 years of age (28, 29), therefore this issue and the comorbidities with which it is associated become important. The main limitation we had in the study was the small population sample, which could be reproduced by expanding the sample size.

Conclusions: Pediatric patients diagnosed with cholelithiasis treated at the San Rafael hospital of Tunja between 2010 and 2019, presented a prevalence of overweight of 35.7% and obesity of 21.4%, most of them were female, with an average age of 15 years and belonging to the urban area. It is highlighted that within the study population, the case of a patient with Mirizzi syndrome was identified, which is considered a complication that appears in approximately 1% of patients with cholelithiasis and is more common in adults, this indicates an alert to a public health problem that requires a set of interventions focused on the management of risk factors of the pediatric population and thus reduce the probability of new cases.

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Behaviors related to chronic non-communicable diseases development in university students

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Abstract

Introduction: The scientific literature has reported the trend of the impact of non-communicable diseases on public health and therefore the investment of resources that infer in the development of a country.

Objective: This study's objective was to identify the presence of behaviours associated with developing chronic non transmissible diseases in university students as a population susceptible to the modification of this trend.

Materials and methods: Cross-sectional descriptive study was carried out on a sample of 375 university students. The STEPwise method was applied to identify risk factors associated with the development of chronic non transmissible diseases, in relation to behavioural measurements identified by means of STEP1. Descriptive statistics and bivariate analysis were applied to determine possible relationships between the variables studied.

Results: Prevalence of tobacco consumption was 7.5%, frequent alcohol consumption was 91.5%, and fruit consumption was 96.3%, while vegetable consumption was 95%. Only 48% of the sample practiced intense physical activity. A relationship was found between the male sex, with the consumption of tobacco and the practice of low physical activity.

Conclusions: Behaviours associated with chronic non transmissible diseases such as alcohol and tobacco consumption were identified in university students.

Keywords: Physical activity, smoking, fruit and vegetable consumption, alcoholism, university students.

Introduction

Chronic non transmissible diseases (CNTDs) represent one of the most significant challenges of the 21st century due to their social, economic, and human repercussions, generating a negative impact on the poor and vulnerable population, which affects the sustainable development of a country from the point of view of its productivity (1). Similarly, the scope of sustainable development goals is limited by reducing premature deaths from NCDs by 33% by 2030. (2)

The risk factors for CNIDs are mostly modifiable. These risks are associated with environmental factors, psychosocial factors, lifestyles, behaviours, and habits acquired in adolescence and maintained during university life, (3) behavioural and behavioural risk factors such as smoking, alcohol and unhealthy diets and physical inactivity (4) which are in a first place (5) followed by an increase in the trend to unhealthy diets based on the high consumption of foods rich in saturated fats, trans fatty acids and low consumption of fruits and legumes that are acquired in adolescence and in the context in which they develop (6) prevalent in the university population. (7)

According with Patiño et al.(8) low levels of physical activity, obesity, smoking and metabolic syndrome are the most important cardiovascular risk factors in adolescents. Alcohol consumption is associated with the risk of developing important NCDs such as liver cirrhosis, some types of cancer and cardiovascular diseases. (9)

According to statistics from the World Health Organization in Colombia show that 71% of deaths are caused by non-communicable diseases, 28% cardiovascular diseases, 17% cancer, 7% chronic respiratory diseases, 3% diabetes and 16% other NCDs. (10)

This paper aims to contribute to the discussion on this topic, in order to identify risk behaviours or threats that can be reduced or prevented from the university context.

Materials and methods

Design: A cross-sectional descriptive observational study, developed in university students of the city of Neiva Huila, Colombia during the period 2014-2015, with non-probability sampling.

Population:

A total of 15,889 students from 5 universities were identified and enrolled in the first semester of the academic year. This criterion was determined taking into account that the transition from secondary school to higher education implies a significant change in life, including unfavourable changes in behaviours related to eating habits, health and weight gain for many students. (10), (7)

The study selected 375 students who met the following inclusion criteria: be 18 years of age or older, be enrolled in any face-to-face program at public or private universities in the city of Neiva, be in first semester of school and agree to participate in the study by signing informed consent and completing the STEPwise questionnaire (Step 1 Behaviour Measurements). Students attending higher semesters and those who reported being diagnosed with a chronic non-communicable disease were excluded.

Instruments: The STEPwise method was used as a source of information, specifically the STEP1, which estimates the relationship of behavioural measurements for the monitoring of risk factors for non-communicable diseases, a validated and free-to-use tool of the World Health Organization (11). This tool covers information in the main section on: tobacco consumption, alcohol consumption, diet, physical activity in leisure time.

At the procedural level only the basic questions of the instrument were taken into account: tobacco consumption, alcohol consumption, physical activity in leisure time.

The instrument was applied by students of the Physiotherapy program belonging to the research hotbed Visionaries of Science of the María Cano Neiva University Foundation who were trained for its application, after performing a pilot test.

«The study selected 375 students who met the following inclusion criteria: be 18 years of age or older, be enrolled in any face-to-face program at public or private universities...

Statistical analyses: The data was processed in the SPSS version 21 statistical package, descriptive statistics and bivariate analysis with the calculation of statistical Chi-square and OR (95% CI) to determine possible relationships between the variables studied.

Ethical considerations

The research was approved by the research committee of the María Cano University Foundation Act # 001 with code assignment # 01300416-2014-311.

The general principles of the Helsinki Declaration were taken into account by protecting the integrity, privacy and confidentiality of the participants, taking into account that the research had an eminently scientific purpose (12), and was also framed within the guidelines of resolution 008430 of 4 October 1993 in the category of research with minimum risk (13), with regard to the participants an informed consent was drawn up which explained the objectives of the research.

Results

Of the total number of subjects in the study sample (n=375), 242 (64.5 %) were female. The median age was 20 years. As for the socioeconomic stratum, most of the participants were located in the low and medium low stratum, belonging to a subsidized health regime and health and engineering programs.

There was a prevalence of tobacco consumption of 28 (7.5%), alcohol consumption in the last year 343 (91.5%), and 267 (71.2%) in the previous 30 days.

361 (96.3%) university students consume fruit, 356 (94.9%) consume vegetables, and 180 (48%) do physical activity in their free time (Table 1).

Table 1. Behaviors related to chronic non transmissible diseases in university students.

	n	%
Do you currently smoke any tobacco products?		
Yes	28	7,5%
No	347	92,5%
Do you smoke daily?		
Yes	23	6,1 %
No	352	93,9 %
Have you consumed any beverage containing alcohol in the last 12 months?		
Yes	343	91.5%
No	32	8,5%
Have you consumed any drinks containing alcohol in the last 30 days?		
Yes	253	67,5%
No	122	32,5%
Fruit consumption		
Yes	361	96,3%
No	14	3,7%
Consumption of vegetables		
Yes	356	94,9%
No	19	5,1%
In your free time, you practice intense physical activity		
Yes	180	48,0%
No	195	52,0%
In your free time you practice some physical activity of moderate intensity		
Yes	204	54,4%
No	169	45,1%

Source: Own source

In the bivariate analysis, a relationship was identified between the male sex, tobacco consumption (OR 4.3; 95% CI 1.89-9.83), and physical activity practice (OR 3.03; 95% CI 1.94-4.7) and an inverse relationship with the variables fruit consumption (OR 0.13; 95% CI 0.038-0.508), vegetable consumption (OR 0.179; 95% CI 0.063-0.51) (Table 2).

«As for the socioeconomic stratum, most of the participants were located in the low and medium low stratum, belonging to a subsidized health regime and health and engineering programs.

Table 2. Behaviors related to chronic non transmissible diseases in university students, according to sex.

	Tobacco consumption		OR	Confidence interval	Chi square Pearson
Sex	Yes	No	4,3	1,89- 9,83	
Male	19	233			13,87, gl 1, *p* 0,000
Female	9	114			
Total	28	347			
	Fruit consumption		**OR**	**Confidence interval**	**Chi square Pearson**
Sex	Yes	No	0,13	0,038-0,508	11,8, gl 1, *p* 0,001
Male	122	11			
Female	239	3			
Total	361	14			
	Vegetable consumption		**OR**	**Confidence interval**	**Chi square Pearson**
Sex	Yes	No	0,179	0,063-0,51	
Male	119	14			12,7, gl 1, *p* 0,000
Female	237	5			
Total	356	19			
	Intense physical activity		**OR**	**Confidence interval**	**Chi square Pearson**
Sex	Yes	No	3,03	1,94- 4,7	25,03, gl 1, *p* 0,000
Male	87	46			
Female	93	149			
Total	180	195			

Source: Own source

Discussion

From this study the presence of behaviours associated with the development of NCD was described in a group of university students. In 2008, the World Health Organization (WHO) established that physical inactivity, smoking, harmful use of alcohol and an unhealthy diet were the behavioural risk factors associated with NCDs (14), conditions that are not alien to the university population and that, on the contrary, make them vulnerable (15). In 2010, such unhealthy behaviours were responsible for approximately 21.5 million deaths worldwide, mainly inadequate eating habits (16).

For the present study, the presence of high alcohol consumption and low adherence to physical activity were the main risk factors associated with the development of NCDs. Contrary to the WHO established in 2008, low tobacco consumption was found, while other studies have recorded a

wide range of smoking prevalence in university students (17). In relation to gender, men are the biggest consumers, similar to what has been reported in previous studies (18), (19), (20). Low consumption in this study could be related to the promotion of tobacco-free environments and educational campaigns for the prevention and reduction of smoking in the university context.

As for alcohol consumption, a high prevalence was found, consistent with the results obtained in the National Study of psychoactive substance use in Colombia, the highest current alcohol use rate, of 49.2%, occurs among young people from 18 to 24 years, and with a value of 45.4%, consumption is defined among young people from 25 to 34 years (21). Salcedo et al., in 2011, found that 73% of university students consumed alcohol (22). Other research suggests that a significant proportion of breast and colon cancer cases may be attributable to excessive alcohol consumption (23). Harmful alcohol consumption in the university population represents a very delicate public health problem because it is associated not only with the risk of suffering NCDs, but also with liver diseases, mental and behavioural disorders (24) that increase the risk of university students to present harmful behaviours with a highly negative impact for their future, such as suicides, injuries, engaging in violent acts (traffic accidents, scuffles) and practicing unsafe sex (22); situations to which alcohol consumers are exposed.

Regarding the consumption of fruits, vegetables and vegetables was found a high percentage in their consumption, similar to the results reported by Restrepo et al (25). By contrast, studies on eating behaviours mostly highlight unbalanced macronutrient intakes and significant nutritional deficits of micronutrients in university students, due to the short time spent by young people on preparing healthy foods and the ease of access to "fast foods" (26), (27).

The results obtained in this study are encouraging, considering that the consumption of fruits and vegetables is considered as a protective factor for the development of non-communicable diseases and for the proper maintenance of the Body Mass Index (BMI) in university students (28).

Finally, it was found that most of the university students surveyed showed little physical activity in their free time, which is consistent with other studies on physical activity in university population worldwide. In the United States, levels of sedentary lifestyle in a study with college students registered 86.6% (29), while a meta-analysis of physical activity behaviours

in college students established percentages between 40% and 50% (30). With respect to gender, university women have lower levels of physical activity than men. This finding has been widely described by the scientific literature in the last decade (31), (17), (32), (15).

Deforche et al., in 2015, stated that low levels of physical activity in university students are the result of an age-related process, as they become less active as time passes in the transition between adolescence and adulthood. Thus, the level of physical activity of the last year of university is predictive of the level of physical activity after graduation and prevails during adulthood (10).

This research presents limitations of cross-sectional studies. In addition, sociodemographic characteristics such as academic and socioeconomic level were not included; which would have been important in the analysis of the results.

Conclusions

This study represents a contribution to the characterization of the lifestyles of university students. We found a high prevalence of alcohol consumption and, in contrast, a low prevalence of tobacco consumption and a low level of physical activity. These findings invite us to continue strengthening strategies to enhance the University as an environment that promotes the health of the educational community, which in turn mitigates the development of future complications and reverses the current upward trend in the development of chronic diseases.

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Años potenciales de vida perdidos y análisis espacial de incidentes viales en peatones de Medellín 2015-2020

Years of potential life lost and spatial analysis of road accidents in medellin pedestrians between 2015-2020

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Abstract

Objective: To describe the Years of Potential Life Lost (YPLL), and the spatial distributions of mortality caused by road accidents in Medellin pedestrians between the periods of 2015-2020.

Methods: A descriptive study with a secondary source of information was carried out, and all the records of pedestrians killed in road accidents were analyzed. The calculation of the YPLL was carried out by five-year age groups and the Life Expectancy at Birth of Colombia as the age limit estimated by DANE for the period 2015-2020 was chosen. To know the geographical distribution of the deaths, point maps, and kernel density estimation with a standard quantile classification were created. The proximity analysis was performed by the multiple ring buffer method, with distances of 100, 200 and 300 meters.

Results: During the years 2015-2020, 696 pedestrian deaths were registered in Medellin, from which 514 (73.9%) were men and 182 (26.1%) were women. The neighborhoods with the highest mortality were Candelaria with a percentage of 31.2% (217 deaths), and Castilla with a percentage of 8.8% (61 deaths). The most frequent injuries were polytrauma with a total of 401 cases (57.6%), and head injuries in 231 cases (33.2%). In total, the city's pedestrians lost 14,553 YPLL due to road accidents. From the total number of fatal pedestrian accidents, 400 (57.5%) of them occurred within a 300-meter radius of a pedestrian bridge.

Conclusion: Male pedestrians had the highest YPLL rates of the period, and they are the ones who die the most on the road. Head and skull injuries

are the most fatal, especially if they are suffered by older adults. The loss of labor and economic power is high for the city, but the social and family loss is incalculable.

Key words: Years of potential life lost, pedestrians, mortality premature, wounds and injuries, accidents, traffic.

Introduction

Walking or walking as a recreational activity in large cities has become a high-risk activity. The lack of infrastructure, signage, public space invasion and disrespect for the rules mean that pedestrians often must share the same space with motorized users, a situation that increases the risk of dying or being injured on the road (1,2).

At the beginning of the twentieth century, cities began a process of urban transformation that encouraged the increase in road infrastructure as a solution to the problem of mobility, under the hypothesis that increasing the road system will reduce the negative effects of mobility, operating costs, and travel times (3,4). Wrong hypothesis that increased the number of circulating vehicles due to improvements in the roads, excessive increase in the speed of circulation and growth in the number of fatal and non-fatal victims due to road incident (4).

In view of the growing problem, the construction of pedestrian bridges was encouraged as a possible solution; the above under the scoop that by segregating pedestrians in elevated structures would benefit their mobility and safety. However, today the number of pedestrians hit continues to increase, and pedestrian bridges have become factors that stimulate the development of high speeds, and together with contextual, citizen safety and accessibility factors make pedestrians choose not to use them (4).

Since the first fatal record of a pedestrian incident on London roads in 1896, and after more than a hundred years, mortality from road incidents has grown to epidemic behavior (5), leaving 1.4 million people dead on roads and highways around the world each year, by low- and middle-income countries being the ones with the highest mortality (5). Half of the people

«During the years 2015-2020, 696 pedestrian deaths were registered in Medellin, from which 514 (73.9%) o were men and 182 (26.1%) were women.»

who die from this cause are vulnerable road users, pedestrians, cyclists, and motorcyclists. Young people die more frequently and prematurely, by the age group of 15 to 29 years being the one with the most deaths (5). Premature mortality due to road incident is avoidable, and like other causes of the same nature prevent or slow down the increase in life expectancy (5).

Walking is a daily necessity for many people in America, a region where 11% of road traffic deaths occur in the world, almost 155,000 a year, the mortality burden is disproportionately assumed by young, poor men with low levels of schooling, who have greater difficulty accessing health care when they are injured, and therefore, less likelihood of recovery and return to work, school or society (5). In Latin America there have been some improvements, especially in institutional management, however, in terms of legislation and user behavior on the roads, the task remains pending (5). To try to reverse this situation, the United Nations (UN) in September 2020 approved the second Decade of Action for Road Safety (DARS) by 2030, and welcomed the conclusions of the 3rd Ministerial Conference on Road Safety held in Stockholm, which recommended the world to migrate from motor and private vehicles to active and public ones, and comprehensively manage speed; ratifying again an unpostponable and unavoidable commitment to reduce by 50% deaths and injuries due to road incidents worldwide, after the failed attempt in the first Decade of Action for Road Safety 2010-2020 (6).

In Colombia in the last decade an average of 6,500 people died per year in road incidents, the mortality rate in 2019 was 14 deaths per 100 thousand inhabitants, and the non-fatal injuries totaled almost 37,000 (7). Medellín capital of the Antioquia department and second city of the country with the highest number of inhabitants, contributed in 2019 the 27% of road mortality, and 55% of the non-fatal injuries of the department (7), the number of pedestrians killed amounted to 80 fatalities (7). By gender, men are more injured than women when they walk around the city (8). 20 years after being executed and sanctioned by the Swedish parliament, Medellín by decree 261 of April 2019, adopted Vision Zero as an approach and strategy to reduce death and road injury (9). Strategy that should have been adopted two decades ago, as a principle and roadmap to meet human goals and commitments to life and the planet.

The recent emergence of global and local pedestrian leagues advocates for pedestrian rights and call for pedestrians to fight for them, trying to

« The database was provided by the National Institute of Legal Medicine and Forensic Sciences (INMLCF by its acronym in Spanish), a benchmark of excellence in Colombia...»

highlight the problem that cities face due to lack of adequate pedestrian infrastructure, and to reduce the risk of exposure when walking (4). This situation evidences the health and inequitable problem faced by cities that requires an urgent change, especially due to the adoption of Vision Zero as a horizon to 2030 where international commitments to life and the environment are assumed, in this case related to the reduction of road death and injury, positioning it as one of the fundamental goals of social transformation and of the same order as other events of surveillance in Public Health. Therefore, the interest of this work focused on describing the Potential Years of Life Lost and the spatial distribution of mortality due to road incident in pedestrians of Medellín 2015-2020.

Methods

A descriptive, retrospective study with a quantitative approach was conducted to describe mortality and Potential Years of Life Lost (PYLL) due to road incident in pedestrians in Medellín; mortality analysis was performed by place of incident and date of death. Secondary information was used, collected through the Information System Network of Disappeared and Corpses (SIRDEC by its acronym in Spanish), technological platform implemented in 2007, in which reports of missing persons and information on corpses subjected to a medical-legal necropsy are permanently recorded (10). The database was provided by the National Institute of Legal Medicine and Forensic Sciences (INMLCF by its acronym in Spanish), a benchmark of excellence in Colombia to quantify mortality caused by road incidents, takes as a basis the records on necropsies performed and filters them to take only those that correspond to the definition of death by road incident (11). The reference population consisted of all the deaths in Medellín recorded in the INMLCF mortality database in the study period; the unit of analysis was the record of each death, where the basic cause of death was classified as violent death and associated with transport events in pedestrian road users. No calculation was made for sample selection, all records that met the following criteria were analyzed: a) violent death in transport; b) the dead

road user was a pedestrian; c) the place of the incident; d) death had been in Medellín; e) during the period 2015-2020. Records of death in transport of other road users were excluded and, for the spatial location of events, records without information, poorly completed or that did not meet geocoding standards were excluded.

To estimate the PYLL, the general methodology set out in the epidemiological literature was adopted, this being an indicator of health impact and used for the study of premature mortality, which illustrates the loss suffered by society as a result of the death of young people or before reaching the maximum life expectancy at birth (LEB) (12). The age limit was the LEB of Colombia estimated by the National Administrative Department of Statistics (DANE) for the period 2015-2020, it was specific by year and gender. The calculation of the PYLL was carried out by five-year groups to ensure the uniform distribution of deaths in each of the age groups (12). The class mark was estimated in each age group, the weighting factor was estimated from the difference between LEB and the class mark, the PYLL were obtained by multiplying the weighting factor by each of the deaths recorded in each age group (12). The Index of Potential Years of Life Lost (IPYLL) is the result of dividing the PYLL and the population projection of the DANE according to age group, gender, and year, multiplied by a constant (12).

The layers of road mesh, neighborhoods, and communes necessary to georeferenced the information were downloaded from the Medellín city maps web catalog, arranged and freely accessible by the Administrative Department of Planning of the Municipal Mayor's Office. The geodatabase of the pedestrian bridges was supplied by the Secretariat of Physical Infrastructure of the city. The analysis and mapping of fatal incidents in pedestrians was done through thematic maps according to the site of the incident; the events were georeferenced by direction of place using the massive geocoder of Medellín "MapGis", which uses a deterministic relationship model through web services, and through a unique identifier allows to distinguish unequivocally the entity (13). Street and road addresses were normalized and standardized according to a deterministic approach (13). The initial percentage of geocoded addresses located in the road network was 96.0%, those not found were reviewed one by one to detect possible inconsistencies, which made it possible to increase the initial percentage of location to 96.3%.

After georeferencing of fatal incidents in pedestrians, a Kernel density map was made. The Kernel Density tool calculates a magnitude per unit area from point or polyline features, thus adapting a smoothly narrowed surface to each point or polyline; allowing to visualize sites with high and low density to identify spatial patterns of mortality or points of greater concentration (14). The Kernel density was classified with the standard-quantile method, which assigns the same number of data values to each class, there are no empty classes, with too many or few values (14).

Finally, the creation of proximity zones with specific distances around pedestrian bridges was carried out by the multi-ring buffer method, with distances of 100, 200 and 300 meters. The result of the use of this tool is the generation of a polygon that surrounds a geometry as a function of a fixed or variable distance, thus allowing the identification and quantification of cases within the selected vicinity. The rings were classified with a color palette that delimits the proximity pattern, with the dark color being the one with the shortest distance from the reference point, and the light one being the one with the greatest (15)

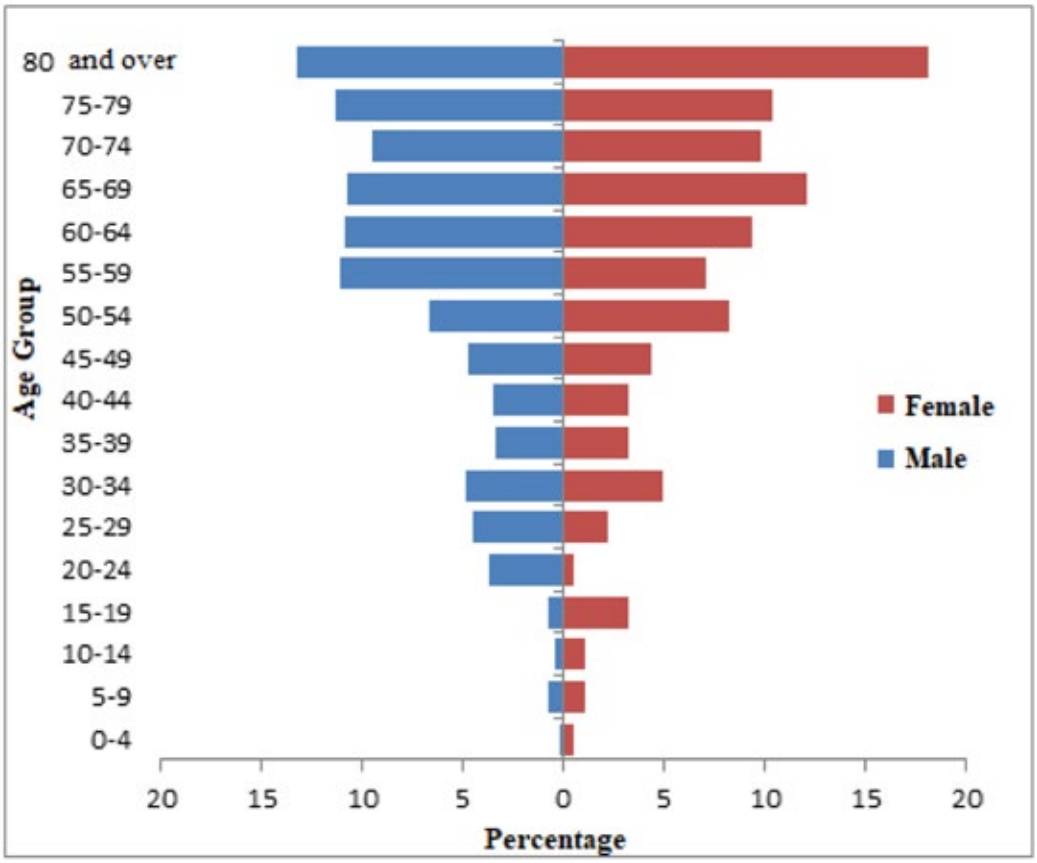
This research followed guidelines and ethical aspects agreed in Resolution 8430 of 1993 of the Ministry of Health, which classifies it in its article 11 as risk-free (16). And the right to personal and family privacy and good name was guaranteed according to Article 15 of the Political Constitution of Colombia (17). For the processing, analysis and presentation of the information, the statistical software IBM SPSS 21®, massive geocoder of Medellín "MapGis", ArcGIS 10®, Microsoft Excel and Word were used.

The limitations are related to the choice of the LEB at the local level as a limit value for the calculation of the PYLL, since these values limit the international comparison, but favor the local and regional comparison adjusted to the population profile of the country.

«This research followed guidelines and ethical aspects agreed in Resolution 8430 of 1993 of the Ministry of Health, which classifies it in its article 11 as risk-free (16).»

Results

In Medellín during the years 2015-2020 the INMLCF registered a total of 696 deaths due to road incident in pedestrians, 514 (73.9%) were men and 182 (26.1%) were women, all killed in two- and more-wheeled motor vehicle accidents. In years, the youngest person at the time of death was 1 and the oldest 97, the 50% of the pedestrians killed were 62 or younger. As the age increases, the deaths due to road incidents in pedestrians increase, by being those over 50 years of age who died the most, with a notorious predominance of women over 80 years of age (Graph 1). The superiority of road death was evidenced in male pedestrians, with a ratio of 3 to 1.



Graphic 1. Mortality due to road incident in pedestrians by age group and gender, Medellín 2015-2020.

The largest number of dead pedestrians had low academic levels: elementary 285 (40.1%) and high school 154 (22.1%), with university level 27 (3.9%), and 1 (0.1%) dead pedestrian with specialization level. It was found 36 (5.2%) cases without any academic level, and 186 records without information. According to marital status, single pedestrians were the ones who died the most 244 (35.1%), followed by those married with 176 (25.3%) deaths. When analyzing the occupations of deceased pedestrians, those who die the most are housewives 78 (42.9%), followed by retired men 56

(10.9%), and unemployed men with 40 (7.8%). There are 14 (2.0%) cases of homeless who died as pedestrians in the study period. By place of the incident, the neighborhoods in which more pedestrians died were in Candelaria with 217 (31.2%) pedestrians killed, followed very far by Castilla with 61 (8.8%) deaths, Laureles Stadium with 58 (8.3%) deaths and Aranjuez with 48 (6.9%). In townships, four of the five townships that the city has presented mortality due to road incident in pedestrians, the highest record was in San Cristóbal with 16 (2.3%) deaths, and the lowest in San Antonio de Prado with 11 (1.6%) pedestrians killed (Table 1).

Table 1. Sociodemographic characteristics of pedestrians killed in road incident, Medellín 2015-2020

Variables	GENDER				TOTAL (N=696)	%
	Male (n=514)	%	Female (n=182)	%		
Academic level						
Elementary	204	39,7	81	44,5	285	40,9
High school	113	22,0	41	22,5	154	22,1
Technical/technology	11	2,1	1	0,5	12	1,7
Bachelor	15	2,9	12	6,6	27	3,9
Specialization	0	0,0	1	0,5	1	0,1
None	27	5,3	9	4,9	36	5,2
No information	144	28,0	37	20,3	181	26,0
Marital status						
Single	178	34,6	66	36,3	244	35,1
Married	136	26,5	40	22,0	176	25,3
Living common - law	70	13,6	18	9,9	88	12,6
Widowed	29	5,6	40	22,0	69	9,9
Divorced	20	3,9	6	3,3	26	3,7
No Information	81	15,8	12	6,6	93	13,4
***Occupation**						
Housewife	0	0,0	78	42,9	78	11,2
Retired	56	10,9	18	9,9	74	10,6
Unemployed	40	7,8	1	0,5	41	5,9
General services	31	6,0	4	2,2	35	5,0
Seller	26	5,1	6	3,3	32	4,6
Informal seller	21	4,1	5	2,7	26	3,7
Independent	25	4,9	0	0,0	25	3,6
Student	10	1,9	5	2,7	15	2,2
Homeless	11	2,1	3	1,6	14	2,0
None	19	3,7	5	2,7	24	3,4

Township/neighborhood						
La Candelaria	167	32,5	50	27,5	217	31,2
Castilla	46	8,9	15	8,2	61	8,8
Laureles Estadio	42	8,2	16	8,8	58	8,3
Aranjuez	36	7,0	12	6,6	48	6,9
Guayabal	39	7,6	9	4,9	48	6,9
Robledo	22	4,3	13	7,1	35	5,0
Belén	24	4,7	7	3,8	31	4,5
Manrique	18	3,5	8	4,4	26	3,7
Doce De Octubre	19	3,7	6	3,3	25	3,6
La América	20	3,9	5	2,7	25	3,6
El Poblado	12	2,3	5	2,7	17	2,4
Santa Cruz	7	1,4	8	4,4	15	2,2
San Javier	11	2,1	4	2,2	15	2,2
Buenos Aires	13	2,5	2	1,1	15	2,2
Popular	9	1,8	5	2,7	14	2,0
Villa Hermosa	7	1,4	4	2,2	11	1,6
San Cristóbal	8	1,6	8	4,4	16	2,3
San Antonio De Prado	6	1,2	5	2,7	11	1,6
Palmitas	4	0,8	0	0,0	4	0,6
Alta vista	4	0,8	0	0,0	4	0,6

* First ten occupations of pedestrians killed in road incident.

The topographic diagnosis of the injury indicated that 401 (57.6%) of the dead pedestrians suffered polytrauma on their bodies, 231 (33.2%) suffered head injuries, and 14 (2.0%) had chest trauma. The least recurrent lesions were in the lower limbs and face, with 2 (0.3%) and 1 (0.1%) cases respectively (Figure 1). The year of most pedestrian road deaths was 2015 with 147 (21.1%) deaths, august with 75 (10.8%) and Saturday with 111 (15.9%) deaths.

«By place of the incident, the neighborhoods in which more pedestrians died were in Candelaria with 217 (31.2%) pedestrians killed, followed very far by Castilla with 61 (8.8%) deaths...»

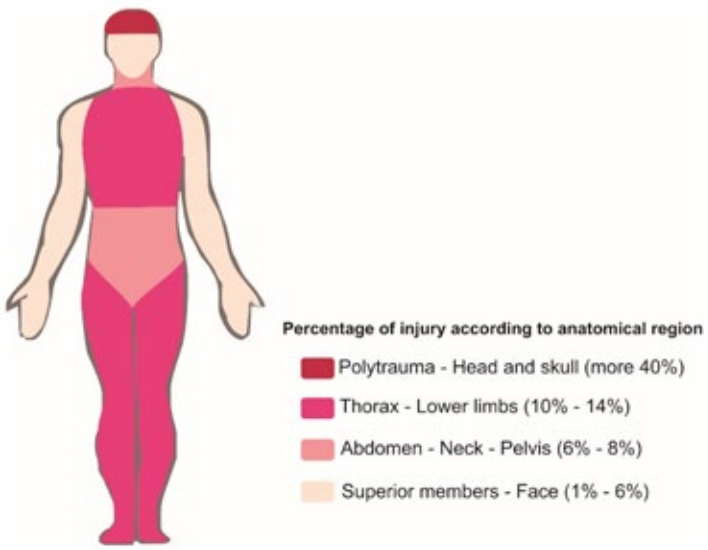


Figure 1. Topographic diagnosis of the injury according to anatomical region of the pedestrian fatally injured in road incident, Medellín 2015-2020.

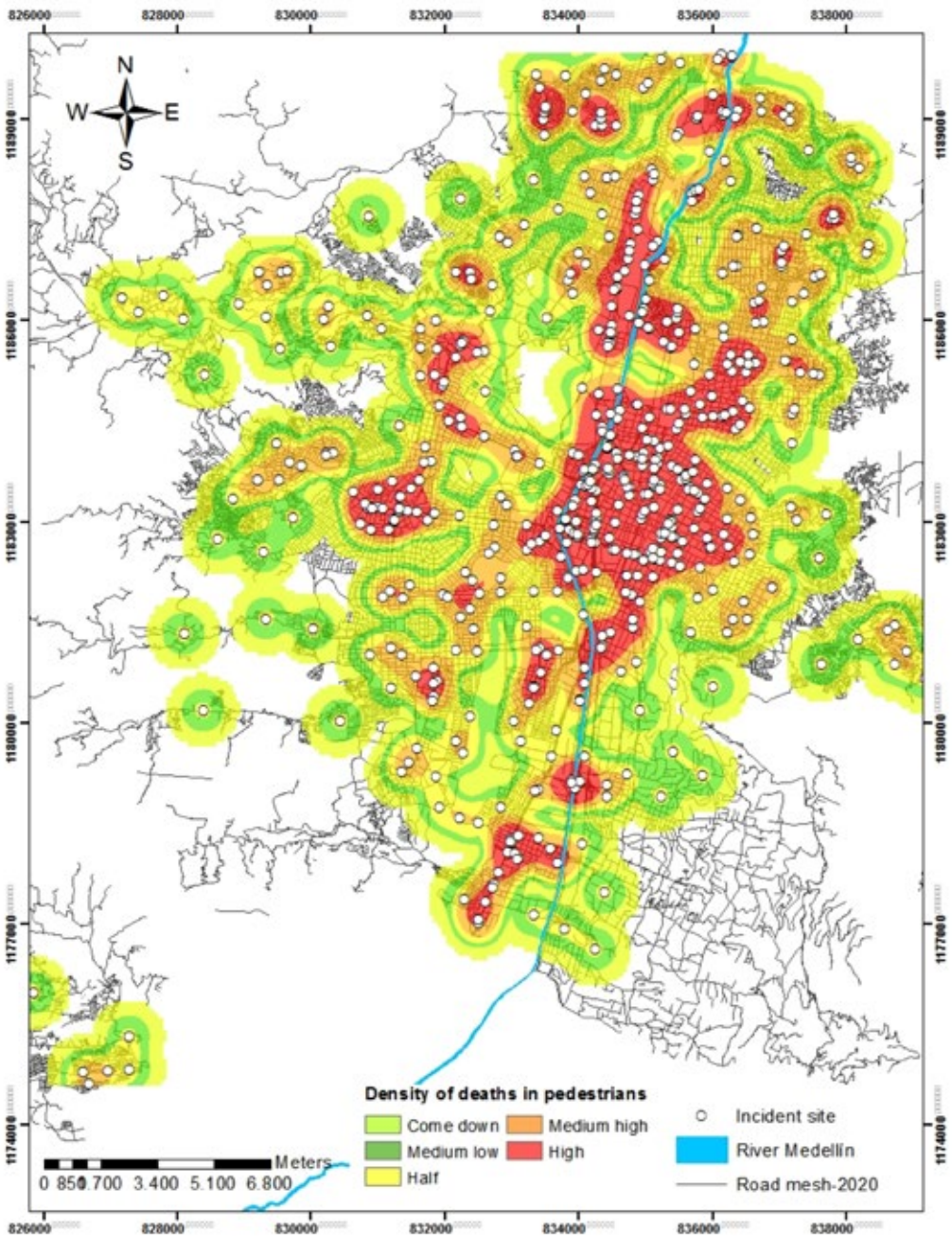
In the five-year study, a total of 14,553 potential years of life were lost due to pedestrians' road incidents in Medellín, which means an index of 104 PYLL per 100,000 inhabitants. Regarding to gender, male pedestrians were the ones who lost the most years of life 9616 PYLL in total, more than double the PYLL in women, who contributed 4172 PYLL in pedestrian road mortality. 2015 was the year in which men contributed the most PYLL 2382 (IPYLL =225 x 100,000 inhabitants), while the highest PYLL in women was registered in 2017 with a total of 805 (I PYLL =65 x 100,000 inhabitants). The years 2015, 2016 and 2017 contributed 55% of the PYLL of the study period, the one with the lowest contribution was 2020, a fact that may be associated with restrictions on mobility due to the COVID-19 pandemic (Table 2).

Table 2. PYLL for pedestrian deaths in road incidents by gender in Medellín 2015-2020

YEAR	Males		Females		Total	
	PYLL	IPYLL	PYLL	IPYLL	PYLL	IPYLL
2015	2382	224,5	613	51,0	3215	143,4
2016	1736	161,7	766	62,9	2641	116,3
2017	1261	115,8	805	65,2	2153	93,6
2018	1462	132,0	736	58,6	2291	97,9
2019	1581	139,5	774	60,4	2481	103,8
2020	1194	103,2	479	36,7	1771	72,8
Total	9616	145,2	4172	55,6	14.553	104,1

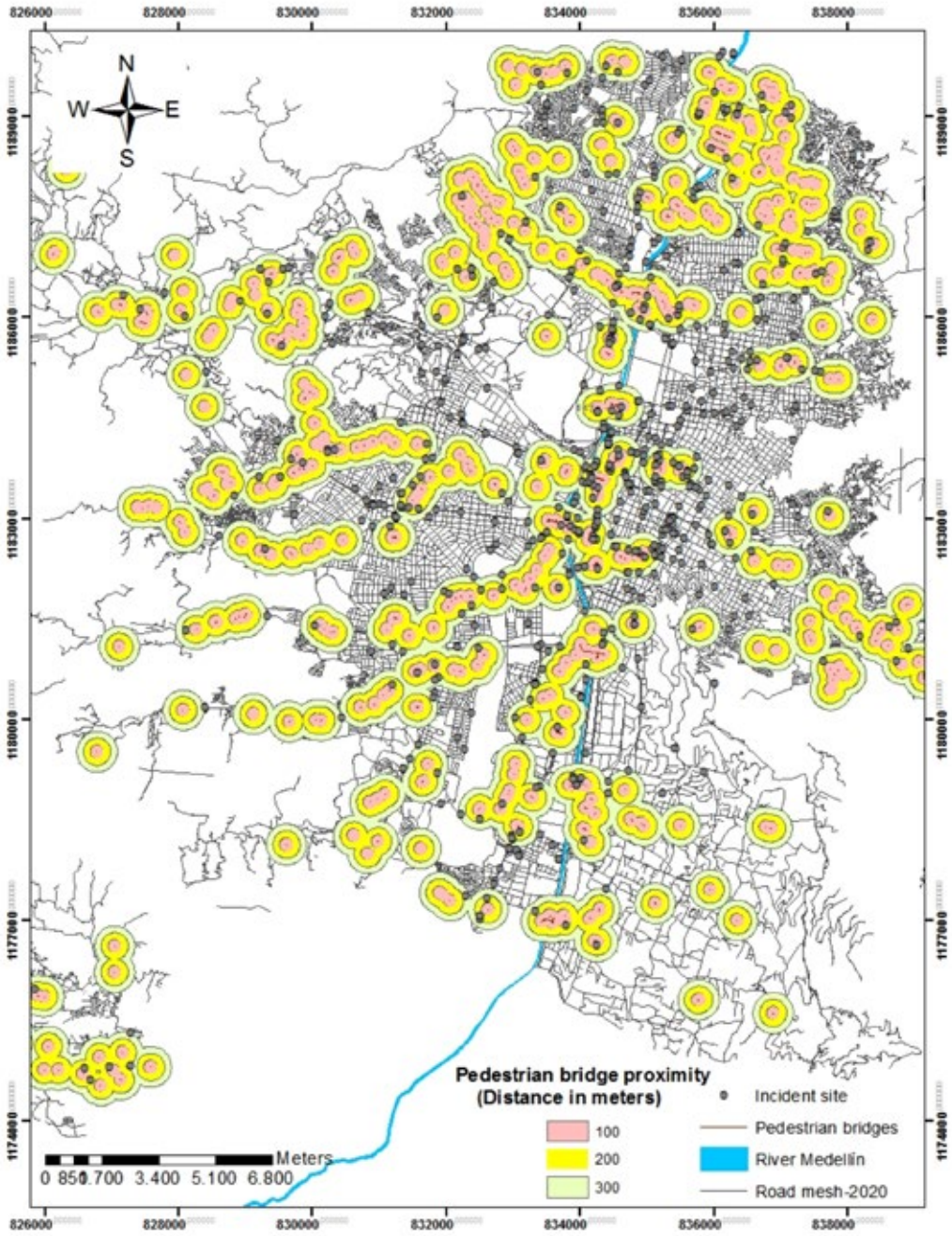
The highest density in pedestrian road mortality occurred in the neighborhood Commune 10, La Candelaria, a downtown area of the city that receives a large amount of people who make their journeys on foot every day. In this Commune, the neighborhoods of San Benito, Corazón de Jesús, Candelaria, Chagualo, Colón, Prado, Boston, Guayaquil and Jesús Nazareno presented the highest density of road deaths in pedestrians (Map 1). Other neighborhoods with high density in pedestrian death were to the north: Caribe, Castilla, and Toscana of the Commune 5 Castilla, to the south Cristo Rey and Santa Fe of the commune 15 Guayabal, and to the west the neighborhoods Conquistadores, Lorena, and Carlos E Restrepo in the commune 11 Laureles (Map 1). By frequency in pedestrian death the greatest happened on roads with a high number of vehicles and that are traditionally poorly classified as highways or "fast" roads, and that lack road infrastructure that protects the lives of pedestrians and other road users. Carrera 62 between streets 44 and 67, was the stretch of road with the highest mortality 34 (4.9%) deaths, followed by street 44 that crosses the city from east to west where 31 (4.5%) pedestrians died.

«Regarding to gender, male pedestrians were the ones who lost the most years of life 9616 PYLL in total, more than double the PYLL in women... »



Map 1. Density of deaths due to road incident in pedestrians in the municipality of Medellín, 2015-2020.

The Secretariat of Physical Infrastructure of Medellín has a registry of 504 pedestrian bridges distributed throughout the urban and rural areas of the city. Of the 696 fatal incidents in pedestrians, 400 (57.5%) occurred within a distance of 300 meters from a pedestrian bridge, 260 (37.4%) at 200 meters and 100 (14.4%) at 100 meters; the remaining percentage of fatal incidents occurred outside the radius of 300 meters (Map 2).



Map 2. Deaths due to pedestrian road incident in influence area of pedestrian bridges in Medellín, 2015-2020

Discussion

In a large percentage of Colombian territory, road incidents are poorly catalogued and misclassified, offering a connotation of accidental origin, making it unforeseeable, unpredictable, and impossible to avoid (18); contrary to their incidental origin, by nature preventable, avoidable, and coming from a continuous incidence that expresses the probability that an individual belonging to a population at risk will develop an event in relation to time

(19). Since 1961 and continuously the WHO has been ratifying that "The accident is not accidental" and expresses its disagreement about the wrong use of the word accident to refer to road incidents (20). Therefore, road incident refers to a situation that is preventable (18), and its incidence could be avoided through public health interventions such as: health promotion, disease prevention, risk communication, specific protection measures and implementation of public, sectoral, and extra sectoral policies (21).

The findings of this study indicate that at an older age increases mortality, a result similar to previous research, where human factors associated with age such as reduced visual acuity, hearing loss, reduced locomotion and environmental factors such as inaccessible pedestrian bridges, lack of accessible crosswalks at ground level, proper signaling, invasion of public space and the short time interval available to cross an intersection, are risk factors that combined with advanced age increase the risk of suffering injuries or fractures in the head with fatal outcome (2). A situation that confirms the state of vulnerability of pedestrians on the road, a fact that is documented in the scientific literature and in the model of safe system as human frailty, a scenario that means that in these age groups mortality is not only the result of a higher incidence, but of a greater lethality, compared to the other population groups (2,22,23). Thus, this study confirms what has been stated in other research, where it is suggested that older pedestrians have more serious injuries, and in case of hospital care require longer periods of hospitalization than young pedestrians (2,22).

In accordance with what has been evidenced at the local and international level on road incident mortality, the results of this study indicated superiority in road deaths of male pedestrians compared to female, contributing 74% of deaths and 66% of the PYLL with respect to the total; similar figures to what was revealed by the WHO for the world, and by Gallego et al for Ecuador, where male pedestrians died more and contributed 64% of PYLL (23); similar figures for the case of Colombia, where in 2020 the National Road Safety Agency indicated that men in the country died mostly compared to women, and contributed on average 80% of premature mortality due to road incident (11).

Polytrauma and cranio-encephalic trauma are one of the main injuries in pedestrians hit by vehicles (24). Head and neck injuries sustained by pedestrians at the time of the incident have been shown to account for nearly 60% of all injuries (24). Another relevant result is the frequency of polytrau-

ma in the topographic diagnosis of the injury, where 58% of the pedestrians who died in Medellín suffered it, a situation that is not distant from what was found in other investigations, where for the particular case of Chile, it was described that the main causes of deaths associated with road incident were linked in 47% of cases to multiple traumatisms, followed by intracranial trauma with 28%, injuries that together explain 75% of deaths due to road incident (25).

Another remarkable result for its magnitude is the loss of potential years of life of pedestrians in economically active age 15 to 64 years, who stopped living 10,500 years, this fact shows the loss of workers for the city's productive sector and the decrease in generated income, not including social and family losses (26.27). There is also a cost for the loss of human capital of young people and adults who did not complete their academic cycle, leaving unfinished the creation of knowledge or business generation (26,27), so the impact of road death for society and life expectancy is high. The economic cost of road incidents in Medellín in 2019 was estimated at COP$ 922,030 million, a very high and scandalous figure for a problem that is preventable (28).

The streets and sidewalks of cities are useful for many things, part of the space intended for pedestrians has multiple uses that limit the traffic of its citizens, making walking from urban centers an unsafe and dangerous activity (1,2,29). The invasion of public space by street sellers, beggars, illegal activities and the presence of construction materials, or poorly parked vehicles block and constrict pedestrian traffic (1), which means that people must travel on the same road as motor vehicles, thus increasing the probability of being injured or killed in a road incident (2,29). This is confirmed by figures from Latin America, where the segment with the highest risk of injury or death in a road incident occurs in pedestrians with 23% of the total road deaths in the region (5). Rapid urbanization, high road mortality and the city designed for the automobile as an axis of development made cities rethink and begin to develop as walkable, accessible, and universal cities, giving priority to pedestrians and non-motorized ways of mobility (1). These transformations are usually crossed by social determinants of health, which by being intervened are expected to significantly result in healthy environments, reduced risk, and increased life expectancy.

This study shows the inequalities and inequities when moving, as evidenced in Mexico, where the level and forms of urbanization could explain

« In conclusion, male pedestrians presented the highest rates of PYLL of the study and are the ones who die the most on roads in Medellín.»

the differences in mortality according to road users (1,4). The relationship between pedestrian behaviors and environmental characteristics are an indispensable factor in determining the usability of urban infrastructure, especially pedestrian bridges, the reasons for their use or disuse are directly related to the ability of pedestrians to cross them (4). To this date, there are no or few studies that evaluate the accessibility, vulnerability, and social exclusion that these infrastructures can represent for people with disabilities, reduced mobility, the elderly, pregnant women, children (4). Therefore, modifying urban architecture reduces the risk of death in pedestrians and other road users, among other reasons, because changes in the environment improve behaviors and enable a cultural transformation (1,29).

In the Mobility Plan 2014-2020 of Medellín, it is proposed local actions and goals to reduce road deaths, identify aspects related to the mobility of the city such as: vehicular saturation of the road system, little integration in means of transport, high rate of road incidents and absence of the pedestrian mobility component in road planning, evidencing a critical situation in the downtown of the city, which shows high vehicular flow and invasion of space for pedestrian traffic (30); this is related with the geographical analyses carried out, where the sites of greater density in pedestrian death are those with high vehicular flow, where high speeds develop, or there is greater invasion of public space, pointing out these areas or stretches of road as environments that make the activity of walking an imminent risk. The finding suggests that sites of greatest road death are fully identified, lack of intervention, modification of the environment and road safety education for all participants.

In conclusion, male pedestrians presented the highest rates of PYLL of the study and are the ones who die the most on roads in Medellín. Head and skull injuries are the most fatal, especially if it is older adults who suffer them, and it is these who are at greater risk of death when walking, because personal factors (gender, age, physical limitations) and environmental (signaling, time to cross, speed, accessibility and invasion of public space) affect the decisions of pedestrians, since their road behavior is guided by

the environment and past experiences, causing them to be forced to develop high-risk behaviors that seem common in this type of user. The loss of labor and economic force is high for the city, but the social and family loss is incalculable. The results help entities, policy makers and authorities to design interventions that improve the walkability of the city through the development of infrastructure and educational programs that transform urban centers into walkable, accessible, and universal cities for all its inhabitants.

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Dirofilaria immitis en caninos del medio Sinú: un posible riesgo para la salud pública

Dirofilaria immitis in canines of middle Sinú: a potential risk for public health

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Abstract

Introduction: *Dirofilaria immitis*, is a worldwide distribution parasite that causes progressive cardiopulmonary disease in dogs, which is located in the pulmonary arteries and right ventricle and produces endothelial injury and pneumonia. The parasite is transmitted by mosquito bites to canines, but it may be found in a variety of mammals, including humans living in endemic areas, which turns it into a zoonosis. The infection has been reported in different Colombian regions.

Objective: To determine antibodies against *D. immitis* in dogs of Cereté, Ciénaga de Oro, and San Carlos, municipalities of middle Sinú (Córdoba).

Materials and methods: Blood samples of 105 crossbreed dogs were collected from the urban areas of these municipalities in order to conduct a descriptive cross-sectional study and stratified sampling. Antibody to *Dirofilaria immitis* was measured through the implementation of an enzyme-linked immunosorbent assay (ELISA). Descriptive analysis and Chi-square were used to determine whether there were significant differences with respect to *D. immitis* seropositivity and the parameters investigated (age, race and geographic region of origin).

Results: The seroprevalence to *D. immitis* was 5.7%, and the antibodies

were detected in the municipalities evaluated. No statistically significant differences were observed between the seropositivity of different age groups, races, sexes, and municipalities.

Conclusions: The presence of circulating antibodies of *D. immitis* in dogs together with the agroecological conditions of middle Sinú, allows the presence of mosquito vectors involved in the transmission of the disease, wich may represent a potential public health risk in where humans can act as aberrant hosts.

Keywords: Antibodies, antigens, diptera, epidemiology, nematodes, zoonoses (Source: DeCS).

Introduction

The objective was to determine antibodies against D. Immitis in canines of three municipalities of the Middle Sinú (Cerete, Ciénaga de Oro and San Carlos) in Córdoba (Colombia).

Dirofilaria immitis, is a parasite that produces progressive cardiopulmonary dirofilariasis in canines, which it is located in the pulmonary arteries and the right ventricle and produces endothelial damage and pneumonitis. It is transmitted by mosquitoes bite (vectors) to canines and other species such as: Vulpes vulpes or red foxes (2); Canis latrans or coyotes (3), Canis aureus or jackals (4); in Canis aureus or golden jackals (5), Felis catus or domestic cat, Felis silvestriso or wild cat, Ailurus fulgens or red pandas, Ursidae or bears, Otariinae or sea lion, non-human primates (6) and humans, constituting it as a zoonosis (7).

The vectors of D. Immitis are mosquitoes of the gender Aedes, Culex (8), Anopheles (9), Culiseta (10), Mansonia, Coquillettidia and Psorophora (11), Myzorhynchus, Armigeres and Taeniothyncus (11). Currently, Aedes koreicus is an invasive species in Europe, and is likely to be a competent vector of D. immitis (13).

Dirofilariasis disease is of worldwide distribution except in the polar regions, the highest frequency occurs in tropical and subtropical regions where temperature, humidity and vegetation are factors for a higher density of vectors and by the presence of hosts the parasite completes its biological cycle (14). In Greece, mosquito population dynamics have been shown to play an important role in the distribution of D. immitis (15).

Humans have a high probability of becoming infected when they inhabit endemic areas (16), usually they are asymptomatic and the lesions are dis-

covered by radiological examinations when a malignant mass is suspected in the chest (17;18), or cases of unusual location such as in the spermatic artery (19), in hepatic nodules (20), at the intraocular (21), scrotal (22) or in the eyeball (23).

In Colombia D. immitis has been reported in different regions of the country; antibodies against D. Immitis were detected in an indigenous community name Tikuna in the Amazon, Colombia, (24). In Bucaramanga, Colombia, a seropositivity was reported to D. Immitis in humans and canines in the same area (25); cases of human pulmonary dirofilariasis have also been reported (26). The parasite has also been found in high-altitude cities and cold climates (27). By serological tests (28;29;30), case reporting (31), molecular techniques (32), combination of serology and molecular tests (25;32); these results can confirm the adaptability of vectors to different environmental conditions (33).

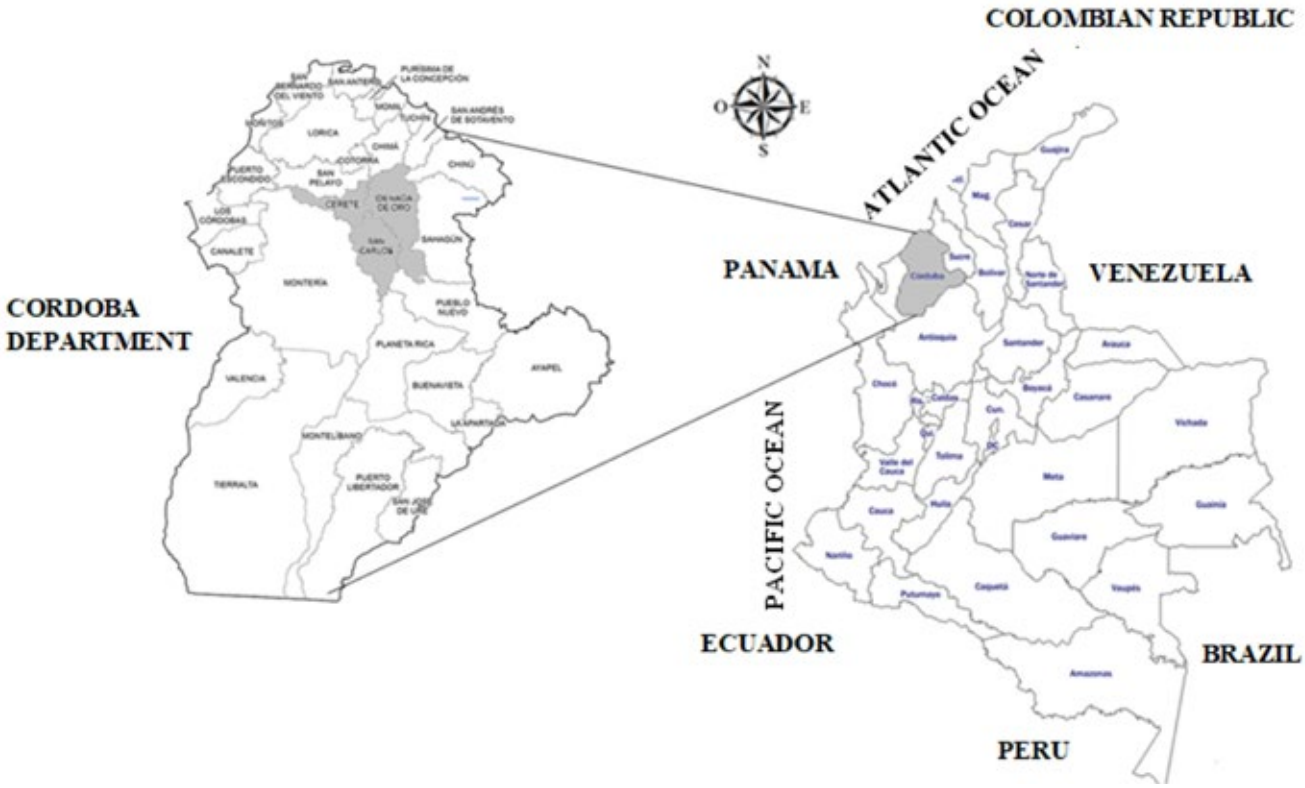
Materials and Methods

Type of study: Descriptive study of cross-sectional cut.

Study area: It was carried out in the urban area of the municipalities of Cereté, Ciénaga de Oro and San Carlos (Córdoba), this are in the geographical region of Medio Sinú (Figure 1).

«In Colombia D. immitis has been reported in different regions of the country; antibodies against D. Immitis were detected in an indigenous community name Tikuna in the Amazon, Colombia.»

Figure 1. Location of the municipalities where antibodies against D. Immitis in canines were determined: Cereté, Ciénaga de Oro and San Carlos, subregion of Medio Sinú in Córdoba (Colombia).



Sample size: The sample size were 105 canines of different ages according to canine vaccination data from these urban areas which was 14,393 canines. A stratified sampling was carried out with proportional allocation in each municipality according to Table 1.

Tabl2 1. Canine determination according to a stratified sampling with proportional allocation by municipality

Municipality	Target population	Percentage	Number of Samples
Cereté	8729	61	64
Ciénaga de Oro	3938	27	28
San Carlos	1726	12	13
Total	**14393**	**100**	**105**

Sample collection: After disinfection of the forearm area and by cephalic or saphenous vein venipuncture, a 5 ml blood sample was taken in a vacutainer tube without vacuum anticoagulant (red cap); each sample was labeled with the respective identification of the animal and kept in refrigeration between 4o C and 8o C in an polystyrene refrigerator, until it was taken to

the laboratory of the Julio E. Cuervo clinic from the University of Córdoba Berástegui headquarters, where the serum was obtained by centrifugation at 3500 rpm for 5 minutes, which was kept in freezing (-70o C) in Eppendorf tubes until processing.

Sample processing: Commercial SNAPMR test kit was used, which is an enzyme immunoassay for semi-quantitative antigen detection D. Immitis canine in serum, plasma, or whole blood of canines and felines. The sensitivity of the test is 98%, the specificity is of 100% (LC from 85, 96 to 100%) and with a Kappa value of 0.98%. This technology allows the conjugated and the sample to be mixed and then this mixture is added to the device that is activated by releasing the reagents stored inside the device; the interpretation of the results was made by the display of the colors in the window and the manufacturer's instructions were followed.

Statistical analysis: A database in Excel format was developed, the information on the variables of the evaluated canines and the results obtained in the laboratory was recorded. Chi-square was used to determine whether the variables age, race and origin were independent of the seropositivity for antigen D. Immitis, and descriptive statistics were calculated using the SAS software.

Results

The seroprevalence determined for antigen D. Immitis in the 105 canines in the urban areas of Cereté, Ciénaga de Oro and San Carlos (Córdoba) was 5.7% (6/105). In each of the municipalities evaluated (Table 2) the presence of the antigen D. immitis was determined and by the Chi-square test (value=3.159; p=0.790) it was shown that there are no statistical differences (P>0.05) between the seropositivity, and the municipalities evaluated

Table 2. Seroprevalence by municipality of canine evaluated in the Medio Sinú region.

Town/ City	Evaluated Canines		Seropositives		Seronegatives	
	n	%	n	%	n	%
Cereté	64	60.95	2	1.90	62	59.1
Ciénaga de Oro	28	26.67	2	1.90	26	24.76
San Carlos	13	12.38	2	1.90	11	10.44
Total	105	100	6	5.70	99	94.30

In Table 3, the seroprevalence by age is presented, where, by the Chi-square (value=1.286; p=0.733) it was found that there are no statistical differences (P>0.05) between seropositivity and age.

Table 3. Seroprevalence by age of canines evaluated in the Medio Sinú region.

Age (years)	Evaluated Canines		Seropositives		Seronegatives	
	n	%	n	%	n	%
1 – 2	55	52.30	3	2.85	52	49.50
3 – 4	22	20.90	2	1.90	20	19.00
5 - 6	15	14.20	1	0.95	14	13.30
> 7	13	12.30	0	0	13	12.40
Total	105	100	6	5.70	99	94.20

The largest population evaluated corresponded to canines of creole or crossbreed, where it was obtained that for each pure-bred canine three canines of creole or crossbreed were sampled (Table 4); despite this proportion, no statistical differences were found per Chi-square (value=0.403; p=0.525), (P>0.05) for this variable.

Table 4. Seroprevalence by breed of canines evaluated in the Medio Sinú region

Breed	Evaluated Canines		Seropositives		Seronegatives	
	n	%	n	%	n	%
Razas mestizas	80	76.10	6	5.7	74	70.40
Razas puras	25	23.80	0	0.0	25	23.80
Total	105	100	6	5.70	99	94.20

Related to sex, the number of males was slightly higher than the females; likewise, for the Chi-square (value=0.071; p=0.790) no statistical differences were observed (P>0.05) (Table 5).

Table 5. Seroprevalence by sex of canines evaluated in the Medio Sinú region.

Sex	Evaluated Canines		Seropositives		Seronegatives	
	n	%	n	%	n	%
Machos	58	55.20	6	5.7	74	70.30
Hembras	47	44.70	0	0.0	25	23.75
Total	105	100	6	5.70	99	94.20

Discussion

A seroprevalence to antigen D. immitis of 5.7% in three urban areas of Cereté, Ciénaga de Oro and San Carlos (Córdoba), municipalities located in the Middle Sinú region was determined, where the subhumid and humid tropical climate predominates with a monthly rainfall ranging between 110 and 182 mm (34); humid and sub-humid tropical climates are conducive to

the presence of vectors (ticks and mosquitoes) that can transmit diseases (35). It has been determined that humidity and vegetation facilitate the development of mosquitoes (36).

A recent comparative study among Medellín (Andes region), Barranquilla and Cartagena (Caribbean region), the seroprevalence was 0% in Medellín and 3% in Colombian Caribbean cities where the humid tropical climate predominates (29). Previously in the Valle de Aburrá a seroprevalence of 0.35% was reported and it was concluded that in Medellín and the Valle de Aburrá D. immitis is not an endemic disease (28). A clinical case in a three-year-old German Shepherd born in Medellín and moved to the island of San Andrés since it was five months old, reflected an unknown if this archipelago is an endemic area (31).

On the other hand, a study conducted in Girardot (Cundinamarca) with a dry tropical climate, in the non-homeless urban canines, heart disease compatible with D. Immitis (27) was not diagnosed, since prophylactic treatments and better care can decrease exposure to vector-borne pathogens in endemic areas (37). Likewise, other studies have established that significant differences have also been found between homeless and non-homeless canines (38). Moreover, a comparative study among regions concluded that in Colombia no significant differences have been observed between the prevalence and the different geographical regions (39), but the habit of canine wandering the streets led to significant differences being established (40). In shelter canines from metropolitan areas of Bucaramanga (Colombia), a prevalence of 6.3% was determined in blood smear and 0.5% with an immunochromatographic test (30). Finally, another study in the same city determined a seroprevalence of 6.71% in humans living with canines, where the seroprevalence was 5.12% (25).

On this research, no statistical differences were found between seropositivity by municipality (Cereté, Ciénaga de Oro and San Carlos), adjoining municipalities of the Medio Sinú region, where canines have the same probability of becoming infected, because they live in the same region that offers favorable environmental conditions for the presence of vectors. However, the capture of mosquitoes of the gender Aedes, Culex, Anopheles, Culiseta, Mansonia, Coquillettidia, Psorophora, Myzorhynchus, Armigeres and Taeniothyncus have been reported in The Medio and Bajo Sinú (40;41;42;43); although no studies have been carried out to show infection of D. Immitis in these regions.

When the independent variable seropositivity and the dependent variables: race, sex and age were correlated, no statistical differences were determined, which indicates that canines of both sexes, of any race and age and who inhabit the urban areas where the study was implemented, have the same probability of infecting. Very similar results for age and sex have been reported in canines in Iran and other places (44) (45). Significant differences have been determined between pure and mestizo canines, but these differences may be due to prophylactic treatments and better veterinary care (46).

The habitat of humans in these municipalities of Medio Sinú, along with the detection of circulating antibodies in canines of D. immitis, the agroecological conditions of this region, the presence of mosquitoes and hosts can cause humans to be exposed to the transmission of pathogens and be a risk to public health; by which it is necessary to implement vector prevention and measures control.

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Caracterización clínico-epidemiológica del tromboembolismo pulmonar en autopsias del Instituto de Medicina Legal de Medellín 2010-2020

Clinical-epidemiological characterization of pulmonary embolism in autopsies of the Medellín Institute of Legal Medicine 2010-2020

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Abstract

Introduction: Pulmonary thromboembolism (PTE) is a medical complication that has caused high morbidity and mortality for a long time despite having highly effective diagnostic and therapeutic methods for treating it.

Objective: To describe the clinical-epidemiological and anatomopathological characteristics of PTE diagnoses in corpses admitted for sudden death to the National Institute of Legal Medicine and Forensic Sciences of Medellín 2010-2020.

Methods: This is a descriptive study of a retrospective cohort, formed by cases admitted to the Institute of Legal Medicine for sudden death with cause of death to be established, which were diagnosed with PTE. Analyses were performed with frequencies and summary measures in SPSS 27.0.

Results: Out of 46097 medico-legal necropsies performed in the period studied, 164 cases (0.36 %) corresponded to PTE. The average age was 57.0±19.3 years and 51.2% women. 57.9% was natural deaths, 37.2% had trauma and 36.0% presented another circulatory event. In most of the cases, the death occurred at their residence (47.0%) and public roads (25.6%). In terms of thrombosis, 45.1% were of the pulmonary artery and 34.8% of

intraparenchymal pulmonary arteries and 52.4% of the deceased had deep vein thrombosis of the lower limbs.

Conclusion: PTE is an important cause of death in in-hospital and out-of-hospital patients, despite existing diagnostic, pharmacological and non-pharmacological methods for its prevention. The performance of a greater number of clinical autopsies will reveal the true impact of this complication in our environment and improve the quality of patient care.

Keywords: Pulmonary thromboembolism, autopsy, sudden death, embolism.

Introduction

Pulmonary thromboembolism (PTE) is a common and potentially lethal form of venous thromboembolism (VTE). Most patients die from this condition, usually within the first hour of the event, with a lethality close to 10%. The mortality rate of diagnosed and treated PTE varies from 3 to 8%, but increases to about 30% in untreated PTE. In the United States it affects annually between 500,000 to 600,000 people and it is a primary or secondary cause of death in 150,000 to 200,000 of these individuals (1).

The condition is often suspected in patients who present with unexplained dyspnea, tachypnea, or chest pain, and an indistinguishable clinical picture in multiple pathologies. (1,2). Its study is usually performed when clinical findings or a history of high-risk predisposing conditions such as obesity, immobilization, trauma, recent surgeries, pregnancy, malignancy, smoking, oral contraceptives or hormone replacement therapies, and a history of pulmonary embolism or a hypercoagulability disorder are present. However, 30% of patients with pulmonary embolism do not have detectable triggers, although it is useful to indicate that the average age of patients with this event ranges from 56 to 66 years (1,3,4,5,6). In addition, the literature has indicated that for trauma-related cases the greatest increase in its incidence occurs about one or two weeks after the injury, but in other cases there is no relationship with time and its presentation can be insidious and sudden (7).

«This is a descriptive cohort study carried out through the analysis of sudden death cases with cause of death to be established that were admitted at the Institute.»

«Within the initial assessment a pre-test (Wells scale) is performed, this combines the patient's history with present signs and symptoms ...»

Despite the detection and intervention of multiple risk factors, including the intensive use of prophylaxis for deep vein thrombosis with heparins, pneumatic compression devices or pressure gradient measures, PTE continues to be one of the most feared and difficult to diagnose complications in patients receiving medical attention in a health institution. (8), this is a consequence of their broad differential diagnoses and weak sensitivity and specificity of their diagnostic tests (2,9). Within the initial assessment a pre-test (Wells scale) is performed, this combines the patient's history with present signs and symptoms, then diagnostic tests are used that may show non-specific alterations of the disease, but that are often used to rule out other diseases with similar symptoms, among which are arterial blood gases, electrocardiogram, and plain chest x-ray. It is also used in its diagnosis the D-dimer, this is a test of great sensitivity in patients suffering from VTE, but not very specific. The reference test is pulmonary arteriography (2,9,10).

Due to the decrease in the practice of clinical autopsies (probably due to the confidence of doctors in diagnostic images and laboratory tests, despite its limitations of specificity), this disease is not recognized as the cause of death in most fatal outcomes generated by it, therefore in many cases the cause of death is thoroughly unknown (11). Even an exhaustive search in the databases PubMed, Science Direct, Google Scholar, ProQuest and Embase, using the keywords "Pulmonary thrombo-embolism, Epidemiology, clinical-pathological correlation, autopsy" only allowed the finding of 32 articles and few of them were directly related to the topic of this research.

In this regard, Micallef considers that the decrease in the practice of clinical autopsies does not allow studies that provide precise statistics on the mortality rate for PTE due to the clinical diagnosis is still unspecific (11). On the other hand, Nagamalesh's group made a diagnosis of PTE by computerized tomography in 31 hospitalized patients and provided recommendations on its management (1); while Hansma's group carried out a study of thrombi found in 238 autopsies, analyzing their macroscopic and microscopic characteristics in the categories of antemortem, postmortem and agonal thrombus, which help to clarify the cause of death (12). Finally, Carrillo's group clarified the diagnostic sequence of PTE, analyzing the main

diagnostic, clinical, analytical, and imaging tools, with special emphasis on the principles that rule the evidence-based medicine (2).

The above exemplifies the small number of investigations that have been carried out recently on the subject, for this reason this study was conducted with the aim of describing the main clinical, epidemiological, and pathological characteristics of PTE in legal-medical autopsies at the National Institute of Legal Medicine and Forensic Sciences of Medellín between 2010 and 2020. This research is important given the low number of clinical necropsies currently being developed because of the confidence of many physicians in diagnostic imaging and laboratory tests despite their low diagnostic accuracy and the persistence of clinical-pathological discrepancies for diagnosis, among other aspects that require increasing research in this field (11.13).

Methods

Type of study: Descriptive of a retrospective cohort.

Study population: A total of 46097 necropsies were performed by the legal medicine institute of Medellin during 2010-2020, of which 164 were diagnosed with post-mortem PTE. Since all subjects were included, the concepts of sampling and sampling do not apply. All necropsy reports were reviewed. Of the initial cases, 15 cases were excluded in which the necropsies did not meet the requirements for the diagnosis of PTE, that is no clear descriptions or findings were required that led to the diagnosis, it did not include the exploration of the pulmonary arteries, it did not make an identification of the thrombus and omitted to look for its origin that is usually found in the lower limbs. All cases with a history of hospitalization, prior treatment to fatal outcome, basic thromboembolic disease and previous surgeries were included due to these conditions are important for the presentation of the disease and the subsequent analysis of the results of the present work.

Data collection: The source of information was secondary, it consisted of the database of the National Institute of Legal Medicine and Forensic Sciences, Medellín headquarters, where the information generated by the medico-legal necropsies carried out are recorded, System Identification Registry Disappeared and Corpses (SIRDEC by its acronym in Spanish), in this

« The above exemplifies the small number of investigations that have been carried out recently on the subject, for this reason this study was ...»

platform the forensic doctors pour all the information related to variables such as identification data of the deceased, form and cause of death, summaries of medical history and necropsy findings. The Institute carries out quality control of these expert reports through a peer review to have approval for their subsequent printing and sending to the judicial authorities.

Bias control: Selection bias was controlled including all subjects who met the eligibility criteria, the control of information biases was performed by forensic medicine professionals with strategies such as the audit of necropsies by reviewing 100% of the reports. For the control of biases in the extraction of data from the secondary source, double typing and logical verification were performed.

Analysis plan: age (single continuous variable) was described with mean, standard deviation, interquartile range, and range; the other variables were categorical and were described with absolute (n) and relative (%). The database and analyses were performed in SPSS 27.0.

Ethical aspects: The Declaration of Helsinki principles, Resolution 8430 of 1993 of the Ministry of Health of Colombia, the guidelines of legal medicine were applied to ensure that the use of the information was only for investigative purposes and that the analyses are based on data that do not contain information that can lead to the identification of each case, since a legal medicine professional delivers a blinded file (without case identification data).

Results

The average age of the study population was 57.0±19.3 years, with 50% of the central data between 42-72 years and range between 10 and 92. In the municipalities of the metropolitan area 9 were from Bello, 3 from Itagüí and n = 3 from Envigado, the other municipalities included Amagá (n = 2), El Retiro (n = 2), Rionegro (n = 2), Apartadó (n = 2), San Pedro de los Milagros (n = 1), Ciudad Bolívar (n = 1) and San Roque (n = 1). In other socio-demographic characteristics, it was highlighted that the majority were women, married, with a high school education and engaged in occupations classified by the ILO as elementary, such as mason, recycler, or others (Table 1).

Table 1. Sociodemographic characterization of the study population

Socio-demographic variables		n	%
Necropsy Municipality	Medellín	138	84,1
	Others in the metropolitan area	15	9,2
	Others from Antioquia	11	6,7
Sex	Female	84	51,2
	Male	80	48,8
Marital status	Married – Domestic partner	78	47,6
	Single	52	31,7
	Widower	23	14,0
	Divorce	11	6,7
Level of education	None	19	11,5
	Elementary	65	39,6
	High school	66	40,2
	Higher	14	8,5
Occupation	Elementary occupations	51	31,1
	Housewife	38	23,2
	Independent	17	10,4
	Retired	21	12,8
	Unemployed	20	12,2
	Student	6	3,7
	Professional	11	6,7

In the study subjects, 57.9% registered death from natural causes and the remaining percentage from violent causes, in these causes the presence of trauma and events of the circulatory system was more frequent, and the main places where the event occurred were in their homes, public roads and hospital centers (Table 2).

Table 2. Distribution of cases according to form, cause, and place of death

Death cases characterization		N	%
Type of death	Natural	95	57,9
	Violent - Accidental	34	20,7
	Traffic accident	22	13,4
	Homicide	8	4,9
	Violent (without typology)	4	2,4
	Suicide	1	0,6
Cause of death	General trauma	61	37,2
	Other circulatory system events	59	36,0
	Cancer	3	1,8
	Other	12	7,3
	Unspecified	29	17,7
Events scene	House	77	47,0
	Public row	42	25,6
	Hospital	16	9,7
	Farm	3	1,8
	Passenger terminals	2	1,2
	Bars	1	0,6
	Children and nursing homes	1	0,6
	Lodgings	1	0,6
	Hospices	1	0,6
	Mines	1	0,6
	Other – unspecified	19	11,6

In relation with the traumas, the highest proportion of subjects did not register trauma, and the most frequent traumas were multiple and lower limbs; 25% of subjects with previous hospitalization, 15.9% with medical treatments and less than 10% with surgical history were presented. There was a 45.1% of pulmonary arterial thrombosis (riding thrombus) and in 34.8% thrombi were recorded in segmental pulmonary arteries. 52.4% of the deceased had deep vein thrombosis of the lower limbs and 4.3% of the iliac veins (Table 3).menos del 10% con antecedentes quirúrgicos. Se presentó un 45,1% de trombosis arterial pulmonar (trombo cabalgado) y en 34,8 % se registraron trombos en arterias pulmonares segmentarias. El 52,4% de los fallecidos presentaban trombosis venosa profunda de miembros inferiores y en venas iliacas 4,3 % (Tabla 3).

Table 3. Clinical characteristics of the study population

Clinical characteristics		n	%
Topographic diagnosis	No trauma	87	53,0
	Polytrauma	21	12,8
	Lower limbs	29	17,7
	Chest	15	9,1
	Head	7	4,3
	Pelvis	5	3,0
Hospitalization and treatments	Hospitalization	41	25,0
	Treatments	26	15,9
Recent surgical history	Saphenectomy	4	2,4
	Hip surgery	3	1,8
	Abdominoplastic	3	1,8
	Liposuction	2	1,2
	Mammoplasty	1	0,6
	Bariatric	1	0,6
	Laparoscopic	1	0,6
Thrombosis Characterization	Segmental pulmonary artery thrombosis	57	34,8
	Pulmonary arterial thrombosis	74	45,1
	Deep vein thrombosis	86	52,4
	Right or left artery pulmonary thrombi	32	19,5
	Iliac veins thrombi	7	4,3

Discussion

During the period from January 2008 to December 2020, 46097 medico-legal necropsies were performed at the National Legal Medicine Institute and Forensic Sciences in the city of Medellín, of which only 164 cases (0.36%) corresponded to PTE as the cause of death, which is divergent from previous studies in this field. In a 24 years retrospective study (1972-1995) with 16466 necropsies the frequency of PTE was 4.7%; (14); Alikham et al. in their retrospective study between 1991-2000 reported a frequency of 3.9% in 6833 units (15); Sweet et al. reported that between 2002-2012 of a total of 982 cases, 11% were diagnosed as PTE (16); the Mobilia group between 1999-2009 of 10288 studied 1.25% corresponded to PTE (17).

The results of the previously stated studies are much higher than those found in the present study, however it is important to note that, except for

the Mobilia study at the Legal Medicine Institute of Milan, Italy, the other studies were carried out with information collected from hospitals where clinical autopsies were performed, which explains the high number of presented cases. Therefore, the large number of violent deaths treated in our institution compared to the deaths under study due to sudden death, make the figure seem lower, but in fact it is not because in proportion it is related to the finding of Mobilia et al. In this order of ideas, the fact that in the current study it has been found that 57.9% of the deaths taken to autopsy were sudden deaths whose way of death was natural and 36% with underlying heart disease, allows to explain that PTE, as a cause of death outside of trauma, is relevant in its presentation, which is consistent with what has been pointed out in different studies in clinical autopsies (14-16, 18,19,20).

On the other hand, 13.4% of the deaths found in the present study were related to traffic accidents, while many of the studies consulted grouped trauma as a single concept (17,18), which allows us to observe a common variable in Medellín-Colombia and to be taken into account due to the complications of polytrauma and the presentation of PTE in any of the hospitalization stages..

The average age of the deceased for this study was 57.0 years of age and with a similar proportion of men and women, variables that did not present relevant differences with the studies found (14,15,16,17,18,19) except for the study of Kakkar et al. where their analyzed group had an average age of 47 years (20). None of the previous studies (14,15,16,17, 19, 20) took into account the scenario of the facts for their analysis only in one study was allowed to indicate as intra or extra hospital cases (18), the above was due to the fact that the vast majority of studies were carried out with hospitalized patients, but in the present study because they were sudden deaths with a diagnosis to be established, the figures where housing (47.0%) was the place where more deaths occurred, followed by public roads (25.6%) and hospital centers (9.7%), suggest the relationship between sudden death by PTE and its lethality, besides puts on alert in cases where there was hos-

pitalization to avoid its appearance as a trigger for death, because in many cases patients were discharged without contemplating the diagnosis as a complication.

The surgical history found in the present study, related with the previous studies, are important due to while the surgeries performed for orthopedic or other similar types of trauma are predominant in the cases (14, 15, 17, 18, 21), in Medellín the most referred (although in a low proportion) were related to cosmetic surgeries, which have increased in the last decade in the city and puts in alert to take into account the previous coagulation states of patients and the performance of related examinations such as PT, TPT, D-dimer for example.

Related to patients who required hospitalization (25.0%) in this study, 15.9% received treatment for the prevention of thrombus formation and even with that they die by PTE, which agrees with the studies reviewed (16, 22,23,24,25), this also allows us to suspect that the presence of PTE, even in patients with antithrombolytic therapy, remains a constant or event of high prevalence for which efforts to perform timely management should be increased; at the same time that measures must be increased to reduce its presence, since the existing ones have not been sufficient.

The finding of deep vein thrombosis in the lower limbs was 52.4% very similar to the finding of other authors (25,26); in relation to riding thrombi (located between the right and left pulmonary arteries) the finding was presented in 52.4%, very close to the findings of Golin et al. 68 % (14), and lower than Nakkar et al. 10.69 % (20), and according to the revision made by Ro et al. (25). Therefore, its suspicion and timeliness in diagnosis is of high importance within the management of groups at risk of presenting the complication.

The present study allowed to observe the presentation of PTE through sudden deaths that reached a legal medical necropsy in order to establish a diagnosis of cause of death and therefore it results into a limitation, since it would be important to contrast it with the clinical autopsies carried out in the different hospital centers, a fact that has currently decreased substantially, but that would be of great importance for this type of studies.

«The performance of a greater number of clinical autopsies will reveal the true impact on our environment of this complication and improve the quality of patient care.»

Despite the diagnostic methods present in the arsenal of clinical practice and thromboprophylactic application in hospitalized patients, thromboembolism remains a disease of great lethality and its suspicion must be considered among the risk groups, and it is of high importance to perform autopsies to avoid the final cause of death from being diluted in other pathophysiological disorders and the spectrum of this complex condition be invisible.

Conclusion: PTE is an important cause of death in in-hospital and out-of-hospital patients despite existing diagnostic, pharmacological and non-pharmacological methods for its prevention. The performance of a greater number of clinical autopsies will reveal the true impact on our environment of this complication and improve the quality of patient care.

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Reporte de casos sobre el uso de ácido tranexámico para reducir el sangrado perioperatorio en liposucción y abdominoplastia

Cases report on the use of tranexamic acid to reduce perioperative bleeding in liposuction and abdominoplasty procedures

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Abstract

Introduction: Liposuction and abdominoplasty are two of the most common aesthetic surgeries practiced in the world. One of the most frequent complications of these procedures is the perioperative blood loss, which has negative effects on the recovery of the patients after the surgery. For this reason, it is important to search for new possibilities that reduce blood loss during this type of surgery.

Objective: To evaluate the effectiveness of tranexamic acid in reducing perioperative bleeding in liposuction and abdominoplasty procedures.

Methods: We present a retrospective case series report in which 1 gram of tranexamic acid was applied to a group of patients before the surgery. Later we reviewed and compared an hemogram taken before and after the surgery. Additionally, we evaluate if the patients required blood transfusion after the procedure.

Results: A population of 37 female patients was studied. None of the patients presented a postsurgical hemoglobin level lower than 8 g/dl nor required blood transfusion products after surgery. A Spearman's rank correlation was performed between the variables, in which there was no evidence of association between lipoaspirate, and hemoglobin or postoperative hematocrit.

Conclusion: The tranexamic acid is a medicament that can be useful for reducing perioperative blood loss in liposuction and abdominoplasty, such

results were proved since none of the patients who received the medication required transfusion of red blood cells.

Key words: Tranexamic acid, liposuction, abdominoplasty, hemorrhage

Introducción

Liposuction and abdominoplasty are two of the most performed aesthetic procedures in Colombia and worldwide. The International Society of Aesthetic Plastic Surgery (ISAPS) estimates that in 2018 1,732,620 liposuctions and 888,712 abdominoplasties were performed worldwide (1). Particularly in Colombia, 273,316 cosmetic surgical procedures were performed, of which 17.1% corresponded to liposuctions and 8.5% corresponded to abdominoplasties (1).

One of the main complications of these aesthetic procedures is bleeding, which if it is not controlled can lead to inadequate postoperative periods or even death (2). Regarding the pathophysiology of bleeding during this type of surgical procedure, it is known that when performing liposuction with the suction cannulas, blood vessels and adjacent tissue are injured, which produces bleeding (2). Samdal et al proposes 3 ways by which the blood that was extravasated by the tissues and blood vessels injury is lost: An external loss in the liposuction, an internal loss due to the formation of dead space when removing fat and the blood that is in instruments used in surgery such as gauze or compresses (3).

Over the years, new methods have been sought to reduce blood loss since liposuction is one of the most performed cosmetic surgeries and perioperative bleeding is one of its main complications. For this reason, in 1985 dermatologist Jeffrey Klein developed the tumescent liposuction technique in which adipose tissue is infiltrated with a solution composed of lidocaine, epinephrine and large amounts of saline (called Klein's solution) (4). Subsequently, it was shown that this technique reduced the amount of bleeding compared to other techniques, such as dry liposuction (4).

Likewise, over the years, new possibilities have emerged that contribute even more to reducing postoperative bleeding such as tranexamic acid. This drug is an antifibrinolytic agent that inhibits the conversion of plasmino-

«Liposuction and abdominoplasty are two of the most common aesthetic surgeries practiced in the world. One of the most frequent complications of these procedures ... »

gen to plasmin, which prevents the degradation of fibrin and preserves the structure of the clot (5). By this mechanism of action, tranexamic acid could be useful in decreasing bleeding, as it would act in conjunction with Klein's solution reducing blood extravasation.

When reviewing the literature on the use of tranexamic acid in plastic surgery (Medline and Scielo), the evidence is scarce and the articles that were founded expose the benefits of this drug in the management of burns, maxillofacial surgery, and otolaryngology. For this reason, it was decided to conduct a descriptive study with the aim of evaluating postoperative bleeding and the need for transfusion in patients who were administered tranexamic acid during liposuction and abdominoplasty.

Materials y Methods

A retrospective case series report was conducted with the aim of evaluating the effectiveness of tranexamic acid in reducing perioperative bleeding in female patients who underwent abdominoplasty plus liposuction.

a. Population

For the case report, the medical records of the patients who underwent surgery at the "Santa Barbara Surgical Center" clinic in the city of Bogotá between 15/01/2020 and 15/03/2020 were reviewed. For this study, patients who underwent abdominoplasty plus body liposuction were included and whom the application of 1 gr of tranexamic acid during anesthetic induction was reported; the patients who underwent another additional procedure were excluded from the study as well as patients with clotting diseases that increase the risk of bleeding such as some type of hemophilia, von Willebrand disease, protein C deficiencies. Table 1 is shown the eligibility criteria:

Table 1. Eligibility criteria.

Inclusion Criteria	Criterios de Exclusión
Surgery performed: Abdominoplasty + Liposuction	Hypersensitivity to tranexamic acid
Age: 18 – 65	Presence of coagulation diseases
Application of tranexamic acid	Abdominoplasty + Liposuction + Other Procedure
Patients ASA I or II	Male

After applying the inclusion and exclusion criteria, a population of 37 female patients, within the age range between 18 and 65 years, who had no history of coagulation diseases and who only underwent abdominoplasty plus liposuction was obtained.

Once the total number of cases that were going to be reported were determined, it was decided to compare the blood count that was taken before surgery and with a blood count that was taken 12 hours after the procedure. Additionally, the weight of the flap that was resected in the lipectomy, the fluids that infiltrated for liposuction and the fluids that were suctioned were reviewed.

The procedures were performed by a certified team consisting of 1 anesthesiologist, 1 plastic surgeon, 1 surgical technologist and 1 nursing assistant. Additionally, prior to surgery, acute normovolemic hemodilution with 500 cc of blood was performed in all patients, which is replenished with 500 cc of crystalloid in the first hour of surgery. Anesthetic induction was performed as follows: Cisatracurium 0.15 mg/kg as a neuromuscular relaxant, Midazolam 0.05 mg/kg as an inducer along with Fentanyl 1-2 mcg/kg, Lidocaine 1mg/kg and Propofol 1-2 mg/kg. Maintenance of anesthesia was performed with Remifentanil 0.15 to 0.2 mcg/kg/min and Sevoflurane to 1 MAC.

b. Sample size

Due to the descriptive nature of the work, no formal sample size calculation was performed.

c. Statistical analysis

Quantitative variables are presented in the form of averages and standard deviations, while qualitative variables are presented in the form of absolute proportions and numbers. A Wilcoxon range test of related data was performed exploratorily to assess before and after differences in hemoglobin (Hb) and hematocrit (Hto). Finally, a Spearman correlation was performed exploratorily to evaluate the correlation between hemoglobin delta and hematocrit delta with flap weight.

d. Ethical considerations

The institution where these procedures were performed is certified by the Ministry of Health of Bogotá and all patients who participated in the study have a duly completed consent prior to performing the procedure. Based on what was mentioned in resolution 8430 of 1993, we consider that the study carried out is an investigation with low risk since it seeks to report a series of cases (6). On the other hand, by this being a retrospective study, the population of our study was taken as passive subjects those who had no knowledge about the research that would be carried out. Given this, it was decided to comment with the directors of the clinic who authorized

the realization of the same (act of 13/03/20) considering the current regulations on the use of personal data. The data collection was supervised by the information and registration coordinator of the clinic, this in order to ensure the confidentiality and protection of personal data of the patients who participated in the study.

Result

The age of the patients who participated in the study was first compared. It was determined that the mean age of the patients was 39.7 years. The youngest patient who was in the study was 24 years old and the older patient was 64 years old.

By looking at the pre and post surgical blood counts, several results can be obtained. The mean pre hemoglobin was 13.9 g/dl and the pre-hematocrit was 42.1%, while the average post hemoglobin was 10.8 g/dl and post hematocrit was 33.1%.

Having the values of the pre and post blood counts, it was possible to determine the delta of the change of hemoglobin and hematocrit for each of the patients. The mean hemoglobin delta was 3.1 g/dl while the hematocrit delta was 8.99%.

In a single patient, a pre-procedure Hb of less than 12 g/dl was evident. No patient in the study had a post-procedure Hb of less than 8 g/dl. The Hb of lower value that was found after the performance of the procedure was 8.2 g/dl. Likewise, no patient in the study required red blood cell transfusion after the procedure. The infiltrated and sucked liquids were then compared. The average amount of liquids used for infiltration was 4972.9 cc of Klein solution. On the other hand, the average amount of fluids that were suctioned during liposuction was 4356.7 cc. Regarding the balance of fluids between infiltrated and sucked liquids, it was evidenced that in 9 patients it had a negative value (which meant that more fluids were sucked), while in 27 patients the balance had a positive value (which meant that more liquids were infiltrated) and only 1 patient had a balance of 0 (the sucked liquids were equal to the infiltrated liquids).

Additionally, the weights of the flaps were compared. The average weight of the resected flap during the abdominoplasty was 858.3 grams. The highest weight flap was 3540 grams while the lowest weight flap was 200 grams. Table 2 shows the obtain results:

Tabla 2. Resumen de resultados

	Promedio	Valor mínimo	Valor máximo
Edad (años)	39.79	26	46
Hb prequirúrgica (g/dl)	13.91	10.5	16.1
Hto prequirúgico (%)	42.08	25.6	47
Hb post quirúrgico (g/dl)	10.81	8.2	13
Hto post quirúrgico (%)	33.08	25.2	38.4
Líquidos infiltrados (cc)	4972.97	2300	9000
Líquidos succionados (cc)	4356.75	1700	7500
Peso del colgajo (gr)	858.37	200	3540
Delta Hb	3.1	-	-
Delta de Hto	8.99	-	-

Having these data mentioned, it was decided to perform a Spearman correlation between post-surgical hemoglobin and suction fluids, which was 0.056. This means that there is no direct correlation between these variables. Likewise, a correlation was made between the post-surgical hematocrit and the suction fluids which was -0.022, so there is no association and a correlation between the hemoglobin delta and the suction fluids, which was 0.05 so there was no association either. Age was also not correlated with post-surgical hemoglobin since it has an index of -0.23 so there was no association.

Table 3. Spearman correlation.

	Age	Pre Hb	Pre Hto	Post Hb	Post Hto	Infiltrated (cc)	Suctioned (cc)	Flap (g)	Δ Hb	Δ Hto
Age	1.000									
Pre Hb	-0,1419	1.000								
Pre Hto	-0,0471	0,8434	1.000							
Post Hb	-0,2335	0,3295	0,1674	1.000						
Post Hto	-0,0397	0,2667	0,1585	0,9154	1.000					
Infiltrated (cc)	0,0676	-0,2086	-0,2807	0,0369	0,105	1.000				
Suctioned (cc)	-0,0456	0,0425	-0,1867	0,0566	-0,0221	0,6273	1.000			
Flap (g)	-0,0096	-0,112	-0,1505	-0,1685	-0,2203	0,3493	0,3125	1.000		
Δ Hb	0,1282	0,5463	0,5357	-0,5402	-0,5204	-0,1739	0,0592	0,0461	1.000	
Δ Hto	0,0385	0,4434	0,6327	-0,5193	-0,562	-0,2296	-0,0916	-0,0424	0,8198	1.000

Finally, it was decided to make a correlation between the weight of the flap and other variables of the study. The correlation between flap weight

The average weight of the resected flap during the abdominoplasty was 858.3 grams.

and post-surgical hemoglobin was -0.16 so there was no association. Similarly, a correlation was made between the weight of the flap and the hemoglobin delta which had a coefficient of 0.046, so there was no association (Table 4).

Table 4. Other variables correlation.

Patience age	Pre Hb	Pre Hto	Post Hb	Post Hto	Infiltrated	Suctioned	Flap	Hb Delta	Hto Delta	Liquid Balance
33	14,8	45,3	11,6	34,9	3500	3700	380	3,2	10,4	-200
31	13,4	40,7	11,5	33,2	5000	4800	800	1,9	7,5	200
40	14,7	43,2	11,9	35,3	9000	7100	560	2,8	7,9	1900
47	13	39	13	38	4500	3600	430	0	1	900
45	15,3	46,8	10,9	34,4	5000	3000	1100	4,4	12,4	2000
39	13	39	11,1	35	3500	3500	450	1,9	4	0
53	12	38	11,1	36,6	7000	4800	720	0,9	1,4	2200
34	14,1	42,9	11,3	34,1	3500	3100	460	2,8	8,8	400
26	13,6	42,6	10,7	32,9	4000	3000	300	2,9	9,7	1000
56	14,1	43,4	9,8	31,4	2500	1700	300	4,3	12	800
45	14,2	44,5	9,6	28,4	4000	4500	250	4,6	16,1	-500
45	12,1	25,6	8,8	26,7	4800	4600	1170	3,3	-1,1	200
39	13,8	40,4	11,9	35	6000	4900	290	1,9	5,4	1100
41	13,5	43,1	10,2	30,9	7000	6600	2640	3,3	12,2	400
33	14,8	45,3	11,6	34,9	3000	3600	680	3,2	10,4	-600
42	13,1	38,4	11,6	37,7	6500	5900	340	1,5	0,7	600
44	14,4	42,2	10	31,2	5500	3300	200	4,4	11	2200
34	14,1	42,9	11,3	34,1	4500	4000	500	2,8	8,8	500
45	15,3	45,3	12	35,8	4800	4750	1220	3,3	9,5	50
42	15,1	43,7	12,8	38,4	5000	4800	480	2,3	5,3	200
39	15,5	44,1	10,9	33,3	3800	5300	900	4,6	10,8	-1500
40	14,7	45,5	10,8	32,9	3600	3800	280	3,9	12,6	-200
31	14,7	43,4	11,3	35,4	5000	5100	200	3,4	8	-100
37	14,3	46,3	10	30	2300	2000	460	4,3	16,3	300
42	13,8	41,4	10,5	32,7	4000	4500	1600	3,3	8,7	-500
44	16,1	46,8	11,3	36,4	6000	4600	1100	4,8	10,4	1400
32	13,4	38,9	10,3	30,6	7000	6000	3540	3,1	8,3	1000
34	15,1	45,2	11,8	36,9	5000	4200	900	3,3	8,3	800
31	15,2	47	10,4	30,3	6000	6100	990	4,8	16,7	-100
37	14,7	42,8	10,7	30,3	5000	7500	1450	4	12,5	-2500
30	13,5	41,2	11,4	34,5	5000	2200	1100	2,1	6,7	2800
32	13,8	43,3	12,3	38,2	6000	4300	1100	1,5	5,1	1700
47	10,5	34,6	8,4	27,2	6000	4700	1130	2,1	7,4	1300
45	13,2	40,4	8,2	25,6	5700	4950	1020	5	14,8	750
38	12,5	39,7	8,2	25,2	5000	4600	840	4,3	14,5	400
64	13,5	47	10,5	34	5000	2500	700	3	13	2500
33	12,1	37,1	10,5	31,8	5000	3600	1180	1,6	5,3	1400

Discussion

Based on the results previously presented, it can be evidenced that there are significant statistical differences between hemoglobin and pre- and post-surgical hematocrit, since the p-value is less than 0.05 in the Wilcoxon test; This means that post-surgical Hb and Hto show a significant reduction compared to pre-surgical hemoglobin and hematocrit. This result is expected, since in liposuction blood is inevitably sucked. Although a reduction in hemoglobin and hematocrit was seen, no patient required red blood cell transfusion after surgery or had hemoglobin below 8 g/dl, important parameters since they were the objectives that were sought to be achieved with the application of tranexamic acid.

On the other hand, the Spearman correlation show that there was no association between: 1) post-surgical hemoglobin and suction fluids which was 0.056; 2) post-surgical hematocrit and the suction fluids which was -0.022; 3) hemoglobin delta and the suction fluids which was 0.05; 4)Age and post-surgical hemoglobin since it has an index of -0.23; 5) the weight of the flap and post-surgical hemoglobin was -0.16; 6) the weight of the flap and the hemoglobin delta which had a coefficient of 0.046

Previous evidence

Although evidence on the use of tranexamic acid in plastic surgery is scarce (7)(8)(9), interesting studies on this topic can be found. In 2018 in Rio de Janeiro, Brazil, Consanção et al (5) conducted a prospective study in which they wanted to evaluate the effects of tranexamic acid in reducing perioperative bleeding in patients who were going to undergo liposuction. For this, the author divided a group of women into 2 cohorts, an experimental one to which 10 mg of tranexamic acid was applied prior to liposuction and another control cohort that received 0.9% saline only. After surgery, a comparison of hematocrit levels and the amount of blood in liposuction volume was performed. In the end, it was concluded that the experimental group to which tranexamic acid was applied presented higher levels of postoperative hematocrit, less reduction of hematocrit compared to the initial values and lower blood volume in liposuction.

The study mentioned above is very useful as it has similar features to the study proposed in this article. The population of the Consanção study has characteristics like the population of our study, since they are women who undergo liposuction. Additionally, in both studies, hematocrit was used as a measure to define postoperative bleeding.

Despite the similarities mentioned, Consanção's study has important differences from our study. The main difference is that Consanção's research used a control group and an experimental group, which allowed him to compare the results of both groups. Instead, our study only seeks to report a number of cases and no controlled clinical study was done. On the other hand, Consanção used the Klein equation to determine the total volume of blood in the liposuction, while for our study this variable was not considered.

«The main difference is that Consanção's research used a control group and an experimental group, »

Implications for research

The research that was carried out aims to lay the foundations for additional research to expand knowledge about the use of tranexamic acid in cosmetic surgery. We believe that with the findings presented in this study, research can be carried out that involves a larger population or experimental and control groups, since this type of studies would have greater statistical and epidemiological value.

Implications for practice

The results presented above aim to provide health professionals with another possibility in the management of postoperative bleeding in esthetic procedures. As previously mentioned, controlling bleeding during surgery could ensure a postoperative period with fewer complications and greater patient satisfaction. It is important to clarify that the study only raises a possibility of management.

Conclusion

Finally, tranexamic acid is considered to present incipient beneficial results for the management of perioperative bleeding during the performance of abdominoplasty plus liposuction. These results serve as a basis for studies with greater methodological rigor on the effects of this drug on body cosmetic surgery.

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«The research that was carried out aims to lay the foundations for additional research to expand knowledge about the use of tranexamic acid in cosmetic surgery.»

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Patrones de administración de vancomicina en pacientes críticamente enfermos

Vancomycin administration patterns in critically ill patients

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Abstract

Vancomycin is an antimicrobial used in intensive care units for the treatment of Gram-positive cocci infections. The main PK/PD parameter, predictor of vancomycin activity, is the AUC/MIC greater than 400; this is reached with plasma drug concentrations of 15 to 20 mg/l in the context of a patient with normal renal function. In critically ill patients, there are changes in the pharmacokinetic patterns that lead to sub-therapeutic doses of the antibiotic and a requirement for monitoring the vancomycin levels. There was reviewed literature on this field to determine the best vancomycin administration regimen in critically ill patients, and to establish the basic prescription parameters in this population. It was found that continuous infusion of vancomycin was associated with better results since it reached the necessary plasma concentration levels earlier. The loading dose was in the range of 15 to 30 mg/kg and the maintenance dose averaged between 30 to 40 mg/kg per day.

The target plasma concentration of vancomycin used in most of the studies ranged between 15 and 20 mg/l. In conclusion, the continuous administration of vancomycin shows better results compared to intermittent administration. High doses in loading and maintenance are the most recommended since these do not increase the risk of nephrotoxicity. Finally, PK/PD strategies are useful for adjusting the dose of critically ill patients.

Key words: Vancomycin, vancomycin dose, critically ill.

Introduction

Vancomycin is a tricyclic antibiotic produced from Streptococcus orientalis. It has a half-life of 6 to 12 hours, a volume of distribution of 0.4 to 1 L/K, a protein binding of 50 to 55% (1). The distribution to tissues is variable and affected by inflammation and disease states (1). Vancomycin is a compound with a molecular weight of 1450 Dalton. It has no appreciable absorption orally and is eliminated primarily by renal tract with 89 to 90% recovery without changes in urine within 2 hours after administration of a single dose (2).

For several decades, vancomycin has been used for the treatment of infections by Methillin-resistant Staphylococcus aureus, however, the use of this drug is complex due to its behavior based on the patient's own conditions such as age, weight, comorbidities, and especially renal function (3), which cause their pharmacokinetic characteristics to vary the response widely from one patient to another. Vancomycin belongs to the group of glycopeptides, which inhibit the late phase of peptidoglycan synthesis by inhibiting transglycosylation reactions; the primary target of vancomycin is the primary D- ending (4).

The main PK/PD parameter, predictor of vancomycin activity, is the AUC/MIC greater than 400 (5); this is achieved with plasma concentrations of the drug of 15 to 20 mg/l in the setting of a patient with normal renal function and with a MIC less than 1 (5). Monitoring of plasma concentrations should be obtained before the next steady-state dose, that is, before the fourth dose. Monitoring of the peak dose of vancomycin is not recommended (5). Measurement of the plasma concentration of Vancomycin is performed on patients who will receive prolonged treatments for more than 3 days, patients at high risk of nephrotoxicity, patients with unstable pathological conditions and patients receiving high doses of the drug (5).

Patients with critical pathologies experience body changes represented in variations in the water conditions, alterations in the drugs movement and changes in the elimination and metabolism of drugs, which would lead to inadequate antimicrobial concentrations with its respective impact on the clinical response. Similarly, the inappropriate use of antibiotics contributes greatly to bacterial resistance, leading to complications, adverse events, reconsultations and high costs of care. All interventions to improve the quality of prescribing have a positive impact on patient management and the sustainability of health systems (3).

This bibliometric research seeks to know which is the best regimen of administration of vancomycin in critically ill patients, with the aim of determining the basic parameters of the prescription of the same in this population

Materials and Methods.

We searched the literature with the aim of answering the following question: What is the optimal administration regimen of Vancomycin, for critically ill patients? The terms used in the search, both in the English and Spanish languages were Vancomycin dosage, critically ill. The literature search was limited from 2011 to 2021 and used the following search engines: ovid, scopus, pubmed, scielo and Oxford academic. Topic review articles, case reports, meta-analyses, clinical practice guidelines, articles in pediatric and pregnant populations and systematic reviews were excluded from the search. For the evaluation of the articles that were selected, the Strobe declaration was used because all the studies were observational. All the studies were stored in a table containing the type of study, the methodology used and the results of the study.

Results

After searching the various databases, 1561 articles were identified. When applying the exclusion criteria, 55 articles were selected, of which 3 articles were excluded because they were duplicated and 33 articles because they did not contain information that answered the question proposed. The selected articles were critically evaluated with the recommendations of the Strobe declaration, obtaining a total of 19 articles selected for review.

The selected studies were descriptive, observational, retrospective, and prospective. Three important aspects were identified to evaluate in the way vancomycin was dosed in critically ill patients; the first, consisting of the form of administration, either in continuous infusion or in extended or intermittent infusion; the second related to the loading and maintenance dose given to this type of patient and the third the value of optimal plasma concentrations for critically ill patients.

For the form of administration, 4 studies that compared intermittent infusion against continuous infusion were identified. In all four studies, continuous infusion was higher to achieve earlier and more sustained steady-state plasma vancomycin concentrations, with a lower rate of adverse reactions compared to intermittent infusion (Table 1). In three of the four studies, the sample size for the continuous infusion was higher, however, in the study

by Wysocki et al (6) conducted in France, the distribution of patients was more uniform; in this study, 119 patients were enrolled, of which 58 went to the intermittent infusion and 61 to the continuous infusion; the target vancomycin serum concentration was 10 – 15 mg/l for extended infusion and 20 – 25 mg/l for continuous infusion. The duration of the extended infusion was on average 1 hour; the loading dose was 15 mg/K and the maintenance dose was 30 mg/K per day for continuous infusion and 15 mg/k every 12 hours for intermittent infusion. The conclusion of this study is that continuous infusion was associated with better results in reaching the planned vancomycin concentration levels earlier.

Table 2. Comparative articles of loading and maintenance dose in patients receiving continuous vancomycin infusion

Infusión intermitente versus infusión extendida			
Autor	**País**	**Muestra**	**Conclusión**
Wysocki et al. (6)	France	Intermittent: 58 pts. Continuous: 61 pts.	Continuous infusion was more effective in reaching vancomycin concentrations
Blot et al. (7)	Australia (Multicentric)	Intermittent: 18 pts. Continuous: 24 pts.	Continuous infusion was superior compared to intermittent infusion.
Tafelski et al. (8)	Germany	Intermittent: 49 pts. Continuous: 76 pts.	Continuous infusion was more effective with lower rate of ADR*
Van Maarseveen et al. (9)	Países bajos	Intermittent: 27 pts. Continuous: 44 pts.	Continuous infusion was superior to intermittent infusion.

*ADR: Adverse drug reactions; pts. Patients

For the loading and maintenance dose, 7 articles in continuous infusion were identified (Table 2). The sample size of the articles is variable, ranging from 22 to 348 patients; the loading dose used in these studies ranges from 15 mg/k to 35 mg/k, being an effective dose to reach plasma concentrations of vancomycin in most studies, except in Commandeur et al (10), where the loading dose administered to 66 patients was 15 mg/k and the planned objective was not achieved.

In three of the seven studies, a high loading dose (greater than 30mg/K) was used, showing high effectiveness in reaching steady status early. In Spadaro's study (11) the load was much lower, compared to the other investigations, because they sought the optimal dose in critical patients with compromised renal function, managing to demonstrate that the nomogram of dose adjusted to creatinine clearance was adequate to reach plasma con-

centrations. The maintenance dose ranged from 20 to 40 mg/k in the seven studies, being stratified based on renal function as shown by Spadaro (11); all research except the one of Commandeur et al (10) demonstrated effectiveness at the doses used. The study by Jason and collaborators (12) represented the largest sample found with 206 septic patients, where they administered high doses of both loading and maintenance in continuous infusion; finding that steady-state vancomycin concentrations of 20 mg/l were reached early on.

Table 2. Comparative articles of loading and maintenance dose in patients receiving continuous vancomycin infusion.

Infusión continua				
Autor	**Muestra**	***DC (mg/k)**	**DM (mg/K/d)**	**Conclusiones**
Jason A et al. (12)	206 pts.	35	35	High doses reach early VPC.
Carricajo et al. (13)	22 pts.	30	30	The dose was effective to reach the VPC.
Commandeur et al. (10)	66 pts.	15	40 a 60	The dose was not effective in the 50% to reach the VPC.
Baptista JP (14)	104 pts.	15	30	The VPC was reached at the studied doses.
Spadaro S (11)	348 pts.	10 - 15	DCr: >50 ml/min: 28; 20-50 ml/min: 20; 10 a 20 ml/min: 15; <10 ml/min: 5-7.	VPC was achieved independent from renal function.
Lin et al. (15)	26	25	30	Effective in obese pts to achieve VPC.
Cristallini et al. (16)	107	35	20 – 40	Effective dose to reach VPC.

*LD: Loading dose; MD: Maintenance dose; Ccr: Creatinine clearance; pts. Patients; VPC: Vancomycin plasma concentrations.

Eight studies used intermittent infusion as a form of administration of vancomycin; the sample size of the studies ranged from 31 to 280 patients, except for the study by Setiawan et al. (17) which analyzes a pre-existing database of 1000 samples of critically ill patients receiving vancomycin (Table 3). The loading dose used was in the range of 15 to 30 mg/k, slightly lower than that reported by continuous infusion studies and the maintenance dose was given on average between 15 to 20 mg/K every 12 hours. In seven of

«Eight studies used intermittent infusion as a form of administration of vancomycin; the sample size of the studies ranged from 31 to 280 patients.»

the eight studies, steady-state concentrations were achieved at the doses administered, except in the study by Villanueva et al (18) where a sample of 197 patients at a loading dose of 25 mg/k and a maintenance dose of 15 to 20 mg/k every 12 hours, did not achieve the planned objectives. The average time of infusion of the drug was between 60 to 120 minutes.

Table 3. Comparative articles of loading and maintenance dose in patients receiving intermittent vancomycin infusion.

Infusión Intermitente					
Autor	Sample	Charge (mg/k)	Infusion time (Minutes)	Maintenance	Conclusions
Setiawan et al.(17)	10000 muestras	---	120	20 mg/k/ each 12 hours	High doses to reach VPC.
He J. (19)	280 pts.	25	120	* High Ccr: 46 mg/K; Normal Ccr: 35 mg/k	High doses at increased Ccr are adequate
Dinh. (20)	55 pts.	25	90	Low Ccr: 15-20 mg/k/d; Normal Ccr: 50 mg/k/d	High loading dose, to achieve VPC.
Rosini J et al. (21)	99 pts.	30	60	15 mg/k/d each 12 hours	High loading dose to reach earlier steady-state VPC.
Kovacevic et al. (22)	73 pts.	25-30	60	15 mg/k/d cada 12 horas	PK/PD models are useful to reach VPC.
Álvarez CA et al. (23)	137 pts.	15 -20	90	30 mg/k/d	Adequate doses to reach SVC with lower incidence of ADR
Villanueva RD et al. (18)	197 pts.	25	90	15 – 20 mg/k each 12 hours	VPC was not reached
Truong J et al. (24)	31 pts.	25-30	----	-----	High loading doses to reach VPC

* Ccr: Creatinine clearance; pts. Patients; VPC: Vancomycin plasma concentrations; ADR: Adverse drug reactions.

The plasma concentration of vancomycin used in all studies ranges from 15 to 20 mg/l (Table 4), except in the research of Carricajo et al. (13), where a high target of 30 mg/l was used; This research recruited 22 patients whose creatinine clearance was above 50 ml/minute, concluding that the doses used reach these concentrations at steady state in the 24 hours of administration of the drug. Similarly, for the study by Wysocki et al. (6) the target concentrations used were variable, for extended infusion it was 10 to 15 mg/l, while for continuous infusion it was higher (20 to 25 mg/l); these patients were admitted to intensive care with diagnoses of pneumonia in 45% and bacteremia in 35%, the rest with other infectious conditions; however, both forms of administration were comparable in clinical efficacy and safety.

Table 4: Plasma concentrations of the studies.

Autor	Concentración (mg/l)	Autor	Concentración
Jason A et al. (12)	20	Spadaro S (11)	15 – 20
Setiawan et al.(17)	15- 20	Blot et al. (7)	>15
He Juan et al. (19)	> 10 y > 15 CG	Rosini J et al. (21)	>15
Wysocki et al. (6)	IE:10–15; IC:20–25	Lin et al. (15)	15 - 25
Carricajo et al. (13)	30 mg/l	Cristallini et al. (16)	20-30
Commandeura (10)	>25	Tafelski et al. (8)	10-20; 15-20 CG
Dinh et al. (20)	20 – 30	Kovacevic T (22)	15-20
Baptista JP (14)	20 – 30	Álvarez et al. (23)	15-20
Villanueva et al. (18)	15- 20	Truong J et al. (24)	15-20
Van Maarseveen (9)	15-20		

In the study by Tafelski et al (8), broader targets of 10 to 20 mg/l were used for moderate infections, supported under the risk of nephrotoxicity; in severe cases, the target was extended from 15 to 20 mg/l. Both therapeutic objectives were achieved with the doses administered and the route of administration used.

Discussion

Critically ill patients have pharmacokinetic changes that impact the microbicidal effect of antimicrobial therapy. The best parameter for measuring vancomycin is the AUC/MIC greater than 400, being the plasma concentrations of 15 to 20 mg/l the most related to this value and representing the drug concentration in the steady state, with the lowest risk of toxicity. Lower concentrations are accepted in patients with renal failure, however, they should not be below 10 mg/l. There is no clear agreement on the dose to be use; in some cases, adjustment normograms are used depending on the patient's own conditions such as renal function. The recommended dose according to vancomycin monitoring guidelines (2,25,26) is 15 to 20 mg/k every 8 to 12 hours, adjusted according to the result of plasma levels; similarly for critically ill patients, a loading dose of 25 to 30 mg/k (2,25,26) is recommended.

Patients with high-severity pathologies have structural changes in the water compartments, in protein concentrations and in the purification capacity of both renal and hepatic, leading to changes in the concentrations of the drug with an impact on the clinical benefit and the presentation of adverse reactions. Our search found very similar data to what was previously recommended; plasma concentrations in most studies range from 15 to 20 mg/l; some investigations use higher plasma concentration targets

(6,13,10,20,14,15,16), due to pharmacokinetic changes in critical patients and susceptibility to germs in intensive care units.

The loading dose is necessary to reach steady state earlier; on average before the fifth half-life. Loading doses greater than 20 mg/k were found in our search; this is argued in the changes presented by critical patients in renal function. Creatinine clearance is elevated, leading to low plasma levels of drugs that are eliminated by this route; vancomycin, under conditions of hyperfiltration leads to decreased plasma levels.

Studies such as that of Kuti et al. (27) and Pate et al. (28), support the use of vancomycin in intermittent infusion at doses of 4 grams per day for methicillin resistant Staphylococcus aureus (MRSA) with elevated MIC; this data contrasts with our results, where the use in continuous infusion is recommended. Vancomycin has a mixed pharmacokinetic/pharmacodynamic behavior (PK/PD), that is, it is a time-dependent concentration, which makes it have similar characteristics to the beta-lactams, without belonging to this group, having better optimization of its bactericidal action by being in high plasma concentrations above the MIC, which explains the results of the various investigations found in our search.

The maintenance dose found was on average of 30 mg/k a day divided into two or three administrations; which is related to what is recommended in the management guidelines (2,25,26); however, high doses such as those used in the study by Dinh et al. (20) are supported by the changes in hyperfiltration and increased cardiac output presented by these patients. The study by Fernández de Gatta et all. (29) recruited patients with hematological neoplasms with infection by different species of Staphylococcus and different stages of renal function; it concluded that according to the Monte Carlo simulation, high doses of vancomycin of up to 4 grams per day are required, with creatinine clearances greater than 120 ml/minute. High doses of glycopeptide should be considered in cases of infections by Staphylococcus aureus with MIC greater than 1, which correlates in the study of Canut et all. (30), where they took patients from Spain, Belgium and the United Kingdom, with MRSA sepsis, finding that 25% of these infections had a MIC of 2, and the dose of vancomycin required for treatment was 4 grams per day, which was administered 1 gram every 6 hours.

Increased renal clearance in critically ill patients was described in the study by He Juany et all. (19), where they used doses of 46 mg/k day to achieve low therapeutic levels, of 10 mg/l and 15 mg/l for severe cases.

«Studies such as that of Kuti et al. (27) and Pate et al. (28), support the use of vancomycin in intermittent infusion at doses of 4 grams per day for methicillin resistant.»

High doses of vancomycin with low plasma concentration values were used in this study; this is explained by the increase in the elimination of the drug given by the phenomenon of hyperfiltration. This data is similar with the study of Udy et all. (31) where they show that 65% of patients admitted to the intensive care unit have elevated creatinine clearance with subsequent low vancomycin concentrations (p <0.01) when daily doses less than 30 mg/k are used. For the study of Ocampo Martínez et all. (32), a high proportion of insufficient vancomycin concentrations was reported, due to a rapid elimination of the same and a decrease in the half-life of the drug, secondary to hyperfiltration. In addition, low concentrations of vancomycin lead to a decrease in the area under the curve as a pharmacokinetic parameter of absorption and a poor pharmacodynamic response of the drug; the study recommends high doses of vancomycin to counteract this phenomenon. For cases of renal failure with decreased creatinine clearance, the study by Spadaro et all. (11) shows a dose adjustment in accordance with the creatinine clearance values, with no increase in adverse reactions. The target plasma concentration used in this research was 15 to 20 mg/l, however, in patients with dropped glomerular filtration rate, the goal can be extended up to 10 mg/l2 (2).

The risk of nephrotoxicity is associated with high levels of vancomycin, however, in our review no increase in adverse drug reactions was found, even when using high doses of vancomycin, as shown by the study by Jason et all. (12). Intermittent regimens of vancomycin administration show linear increase in the risk of renal toxicity compared to the continuous dose, as shown by Patel's study (28), where vancomycin doses of 1, 2, 3 and 4 grams per day were administered at intervals of 12 hours, with renal function compromise in 10, 16, 25 and 34% respectively.

Dose adjustment strategies according to the PK/PD principles and the Monte Carlo simulation are effective mechanisms to achieve the planned concentrations of vancomycin in critically ill patients. Kovacevic et all. (22) recruited patients who received vancomycin in 1 hour extended infusion, applying PK/PD models, to achieve plasma concentrations of 15 to 20 mg/l;

it concluded that this strategy was effective, and the calculated average dose was 1 gram every 12 hours. PK/PD strategies, at the moment, are widely used to address patients receiving any type of antimicrobial within the context of safe drug use.

Conclusions

The continuous infusion form of administration shows better results compared to intermittent administration; high doses in both load and maintenance were recommended, without increasing the risk of nephrotoxicity. PK/PD strategies are useful for dose adjustment of critically ill patients, with optimal results.

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Uso de Antibióticos y Resistencia Antimicrobiana en la Unidad de Cuidado Intensivo Neonatal

Use of antibiotics and antimicrobial resistance in the Neonatal Intensive Care Unit

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Abstract

Neonatal sepsis constitutes one of the main causes of neonatal mortality in developing countries. Newborns, particularly premature newborns, have a higher risk of bacterial infections that result in frequent administration of antibiotics in the Neonatal Intensive Care Units (NICU), which is estimated to be as high as 70%. The clinical presentation of neonatal sepsis is non-specific, prompting the early use of empirical antibiotic prescription to avoid adverse consequences in the patients. Its non-specificity characterizes it as a challenging diagnostic, this aspect led several authors to design strategies to determine which newborns are true candidates for antimicrobial therapy.

Microbiology is closely linked to clinical practice. Thus, knowing the most frequent bacteria associated with neonatal sepsis will be closely related to the antibiotic spectrum that should be used to treat it. Furthermore, knowledge on basic pharmacology is key inasmuch as the antimicrobial treatment is not innocuous and can be related to an increase in mortality and morbidity. Clinical course and maternal risk factors are associated with the expected responsible germs that are already described in multiple descriptive studies worldwide.

Indiscriminate use of broad-spectrum antibiotics for the management of newborn infections is leading to antibiotic resistance increase. At the same

time, this is related to even higher rates of therapeutic failure with empiric antimicrobial treatment. Based on this, Antimicrobial Stewardship Programs play a determinant role to monitor the changes in local resistance to adjust and homogenize medical practice to regulate the use of antibiotics and mitigate the emergent and threatening antimicrobial bacterial resistance.

Key words: Drug resistance, microbial, neonatology, antimicrobial stewardship, intensive care, neonatal, antibacterial agents.

Introduction

Neonatal sepsis is one of the leading causes of neonatal mortality in developing countries (1) with data that estimates more than one million deaths worldwide each year (2). Approximately 7 cases are reported per 1,000 live births (LB), which increases to 162 cases per 1,000 LB in those newborns with very low birth weight (<1,500 gr) (3).

Newborns, particularly premature newborns, have a higher risk of bacterial infections, so antibiotic management is the most common therapy in NICUs, which is estimated to be as high as 70% (2,4). In addition, the clinical presentation of neonatal sepsis is nonspecific on many occasions, which means that empirical antibiotic therapy is started early to avoid harmful consequences for patients (2,4).

Among the events related to the use of antibiotics in newborns are the alteration of intestinal colonization, the increased risk of colonization by *Candida* and subsequent invasive candidiasis and increased risk of death (2). In addition, there is an increased risk of necrotizing enterocolitis, death, and late onset sepsis with prolonged duration of antibiotics, so antibiotic therapy is not exempt from serious adverse effects in negative culture scenarios. In fact, more than 95% of newborns in the NICU receive empirical antibiotics, but only 1-5% have initial positive blood cultures (4).

The indiscriminate use of broad-spectrum antibiotics for the management of infections in newborns over the years has generated an increase in antibiotic resistance, which in turn leads to higher rates of therapeutic failure with the use of empirical antibiotic therapies. Due to the above, the Antimicrobial Stewardship Programs play a decisive role in monitoring the change in resistance at the local level to adjust and standardize medical practice that can regulate the use of antibiotics and mitigate the emerging bacterial resistance.

Search strategy

The purpose of this document is to review the use of antibiotics in the Neonatal Intensive Care Unit, the role that the Antimicrobial Stewardship

Programs can have and the impact of antibiotic resistance due to their excessive and inappropriate use; additionally, this review will be used as an academic reference for consultation regarding the pharmacological basis of the most commonly used antibiotics in the NICU, with the addition of a proposal for an antibiogram interpretation algorithm that is useful in clinical practice. Therefore, a literature search was conducted between September 20 and September 26, 2020, in order to identify articles whose results were related to antimicrobial resistance in the NICU, surveillance programs for the use of antibiotics and pharmacological schemes frequently used in the NICU. This search was conducted in MEDLINE / PUBMED, SCIENCEDIRECT, Clinical and Laboratory Standards Institute (CLSI), Center for Disease Control (CDC), European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the Infectious Diseases Society of America (IDSA) using the Medical Subject Headings (MeSH) "Intensive care, Neonatal", "Antibiotic use", "Drug Resistance" and "Antimicrobial Stewardship", in the different combinations allowed.

The articles analyzed were chosen between 2010-2020, if an older article had content of great relevance to the subject review, an exception would be made. After reading the abstracts of the available articles, the full text of potentially eligible articles was obtained for a full reading. Of those relevant articles, a review of the references was carried out to identify more articles that were useful to us. The inclusion criteria were human-related articles, descriptive observational studies, topic reviews, and official society statements. Those articles that had duplicate information due to sharing results with other studies and those that by consensus did not contribute to the purpose of this topic review were excluded. A total of 89 articles were considered for reading, of which 62 were used for the development of this document.

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Results

1. Commonly used antibiotic regimens and reason for use in the Neonatal Care Unit NICU

According to the age of onset, neonatal sepsis can be divided into Early Onset Sepsis (EOS) that is characterized by the appearance of clinical manifestations in the first 72 hours of life (5); or Late Onset Sepsis (LOS) which occurs between 72 hours and 7 days of life in term newborns (6). This time of onset of symptoms, together with an adequate medical history and a complete physical examination play a fundamental role in the choice of the appropriate antibiotic (7).

Given the potential negative outcomes associated with neonatal sepsis (8), the antibiotics used to treat this entity usually include beta-lactams such as ampicillin, oxacillin, cefotaxime, piperacillin-tazobactam, and meropenem. Additionally, glycopeptides such as vancomycin and aminoglycosides are also included. Empirical antibiotic therapy should be guided by local resistance patterns, and the most common microorganisms present in each NICU (9).

Currently, the first-line antibiotic therapy recommended for the management of EOS is the use of ampicillin combined with an aminoglycoside, generally a gentamicin, since it covers the most common microorganisms such as *Escherichia coli* and Group B Beta-hemolytic *Streptococcus* (GBS), which are predominant in this age group (10). However, due to the increase of Gram-negative bacilli (GNB) producing extended-spectrum beta-lactamases (ESBL) in this population (11), close monitoring of local susceptibility patterns is required.

An additional advantage of the ampicillin plus gentamicin scheme is the synergistic effect observed in animal and laboratory models for coverage of *Listeria monocytogenes*, which is a pathogen that can cause pathology in this age group and in immunosuppressed patients (12). If meningitis is suspected, cefotaxime can be added as an empirical agent, since ceftriaxone, given the high protein binding in newborns, is not recommended due to the high risk of acute bilirubin encephalopathy and the risk of lactic acidosis (13). Another alternative for initial empirical management has been proposed that

«The use of cephalosporins in this type of patients does not provide any benefit in the antimicrobial spectrum over the combination of other beta-lactams and aminoglycosides.»

includes the combination of ampicillin and cefotaxime. However, there is evidence that in EOS this combination leads to greater resistance by Gram Negative bacteria in NICUs (14,15).

Regarding patients with LOS, different studies have shown that most isolated organisms in this population are susceptible to gentamicin plus flucloxacillin, and gentamicin plus amoxicillin (16). Coagulase Negative *Staphylococcus* (CNS) represents more than 50% of the isolates in this type of patients, but its true contribution to sepsis is not clearly defined since it is not easy to determine if it is a contaminating agent or a true pathogen. CNSs are low virulence organisms that typically cause silent disease, with fulminant sepsis in less than 1% of the cases (17). There is insufficient evidence of the benefit of administering empirical vancomycin for LOS, so its use as a second line or in those patients with a microorganism susceptible to this antibiotic (18) is recommended. The use of cephalosporins in this type of patients does not provide any benefit in the antimicrobial spectrum over the combination of other beta-lactams and aminoglycosides (19). In table 1. we summarize the clinical conditions, etiological agents, treatment of choice, and treatment lengths at which the clinician can be found in the NICU (20).

Tabl2 1. Use of Antibiotics and Antimicrobial Resistance in the Neonatal Intensive Care Unit

Clinical condition	Etiological agents	*Treatment of choice	Treatment length
Early-onset sepsis	- *GBS* - *E. coli* - *Lysteria monocytogenes* - *Other Gram-negative bacteria: Klebsiella, Enterobacter, Citrobacter, Acinetobacter, and Pseudomonas*	Ampicillin + Aminoglycoside	10-14 days
Late-onset sepsis	- *Coagulase-negative Staphylococcus* - *E. Coli* - *S. aureus* - *GBS*	Ampicillin + Aminoglycoside or Cefotaxime	10-14 days
Meningitis	**Early start** - *GBS* - *E. Coli* **Late start** - *Coagulase-negative Staphylococcus* - *Gram-negative bacilli*	3rd generation cephalosporins: cefotaxime	14-21 days
Pneumonia	- *GBS* - *S. pneumoniae* - *Nontypeable H. influenzae* - *S. aureus* - *E. coli*, - *Klebsiella*	Empirical: Ampicillin + Aminoglycoside Consider additional Vancomycin to cover MRSA	7-10 days to uncomplicated Pneumonia
Urinary tract infection	- *E. Coli* - *Other Enterobacteria: Klebsiella,* - *Enterobacter, Proteus, Citrobacter, Salmonella and Serratia.*	Empirical: Ampicillin + Aminoglycoside Hospitalized patients with late-onset infections: Vancomycin + Aminoglycoside to cover CNS and MRSA	7-14 days
Osteomyelitis and septic arthritis	- *S. aureus* - *E. coli* - *GBS*	Vancomycin + Aminoglycoside or 3rd generation Cephalosporin.	4-6 weeks 8 weeks for MRSA osteomyelitis
Conjunctivitis of the newborn.	- *S. aureus* - *Nontypeable H. influenzae* - *S. pneumoniae* - *Enteric gram-negative bacilli* - *GBS* - *N. gonorrhoeae* - *Chlamydia trachomatis* - *Herpes simplex virus*	Ointment or solution topical antibiotic	7-10 days N. gonorrhoeae: Single dose of IM o IV Ceftriaxone. Chlamydia: Oral erythromycin for 14 days or azithromycin for 3 days.
Omphalitis	- *S. aureus* - *Group A Streptococcus* - *GBS* - *Gram-negative bacilli: including E. coli, Klebsiella and Pseudomonas*	Antistaphylococcal penicillin + Aminoglycoside. If high prevalence of MRSA: Vancomycin instead of antistaphylococcal penicillin.	10 days

*Antibiotic treatment schemes in neonatal infections (20). GBS: Group B Beta-hemolytic Streptococcus, MRSA: Methicillin-resistant Staphylococcus aureus, CNS: Coagulase Negative Staphylococcus..

2. Antibiotics pharmacology used in the NICU

The most commonly used antibiotics in the Neonatal Care Unit are grouped into three major groups: a) beta-lactams; b) aminoglycosides; c) glycopeptides. Each group is presented below, and the mechanism of action is described:

A. Beta-lactams:

a Penicillins:

- Aminopenicillins: ampicillin, amoxicillin
- Isoxazolylpenicillins: oxacillin
- Ureidopenicillins: piperacillin

b Cephalosporins:

- 1st generation: cephalexin, cefazolin, cephalothin
- 3rd generation: cefotaxime
- 4th generation: cefepime

c Carbapenems:

- Meropenem
- Imipenem

Action Mechanism: bactericidal agents that act by inhibiting the synthesis of the bacterial cell wall by inhibiting transpeptidation in the final stages of the synthesis of peptidoglycan, an essential polymer for the bacterial wall. This alteration produces the activation of autolytic enzymes that cause the destruction of the bacteria. Due to their mode of action, they always act in the cellular reproduction phase, so they are not effective against latent forms or against organisms that do not have a bacterial wall (21,22).

B. Aminoglycosides

- Gentamicin
- Amikacin

Action Mechanism: Once in the cytoplasm, they bind to the 16s RNA at the 30s ribosomal subunit, altering the translation of the mRNA and therefore leading to the formation of truncated or non-functional proteins (23).

The mechanism of the bactericidal activity of gentamicin has not yet been fully elucidated, but it is proposed that the truncated proteins are placed in the cell wall, compromising the permeability of the membrane. Others also suggest that the accumulation of reactive oxygen species can lead to bacterial death (23).

B. Glycopeptides

- Vancomycin

Action Mechanism: exerts its bactericidal effect by inhibiting the polymerization of peptidoglycans in the bacterial wall. This binds to D-alanyl D-alanine thus preventing the synthesis and polymerization of N-Acetylmuramic and N-Acetylglucosamine within the peptidoglycan layer. This inhibition weakens the bacterial cell walls and ultimately causes the leakage of intracellular components, resulting in the death of Gram-positive bacterial cells (24).

3. Most frequent germs in the UCIN

The most common pathogenic microorganisms in cases of neonatal sepsis in general are: *Klebsiella spp*, *methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Staphylococcus spp*, *Neisseria meningitidis*, *Streptococcus spp and E. coli* (1,3). GNB account for almost half of all blood cultures from newborns (1,3) .

EOS is caused in 43% by GBS, followed by E. coli in 29% (2). On the other hand, LOS is caused in 70% by Gram-positive microorganisms, mainly by CNS (48%) and S. aureus (8%). Although LOS due to GNB is less frequent (23%), it is associated with higher mortality (19-36%) (2,4).

In a study carried out in Mexico with patients who had EOS and LOS, it was found that the most frequent bacteria in EOS are Enterobacteria (67.6%) and Streptococcus spp. (17.6%) (25). In the case of LOS, Enterobacteria also occupied the first place (44.9%), with Klebsiella pneumoniae by being the most common microorganism, followed by Staphylococcus spp. (34.7%). Of the isolated nosocomial enterobacteria, 40% were found to be ESBL producers (25). Similar findings have been found in other studies (26).

Dharmapalan et al. reported in their work that approximately half of the isolates of *S. aureus* were *methicillin-resistant*, and in the case of Gram-negative germs, high rates of resistance were reported for ampicillin, gentamicin, and cefotaxime in *K. pneumoniae* and *E. coli* (27).

4. Most frequent NICU germs resistance can develop to the most frequently used antibiotics

Antibiotic resistance can be generated by inappropriate treatment durations, an insufficient antibiotic concentration at the site of infection, the use of poor-quality antibiotics, or misuse / overuse (28). The increase in antibiotic resistance in both Gram-negative and Gram-positive pathogens involved in infections of newborns hospitalized in the NICU, generates limitations and difficulties in the proper management of these patients, which leads to an increase in the neonatal morbidity and mortality (1,28).

a. Gram-Negative Bacilli

Among the most common cultivated species of GNB *are Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*.

In Latin America, Klebsiella spp., *Escherichia coli*, and *P. aeruginosa* are the most frequently isolated germs in the neonatal population. General infection rates in NICU and pediatric ICU are of concern, which are higher in Latin America compared to developed countries (5-36% vs 6-15%). In addition, one third of NICU patients die, with a higher incidence in low birth weight newborns and those with GNB infections (29).

These pathogens are often resistant to at least one class of antibiotics used as standard in the treatment of newborns, including beta-lactams and aminoglycosides. Among the mechanisms of resistance expressed are the production of enzymes that inactivate or alter the target site of the antibiotic (e.g., beta-lactamases, carbapenems, aminoglycoside-modifying enzymes), decreased antibiotic permeability (porin closure) and removal of the antibiotic within the bacterium (expulsion pumps) (28,30).

The resistance expressed by *E. coli* is multifactorial and is mainly due to the production of beta-lactamases, which are enzymes that mediate the destruction of beta-lactams by hydrolysis. An increase in the prevalence of *E. coli* strains with ESBL has been observed which give them resistance against penicillins, cephalosporins (first to fourth generation, except for cefamicins), and aztreonam, making them a challenge for treatment. Resistance through AmpC-type beta-lactamases also occurs in strains of *E. coli* but is less common than ESBL production. AmpC-type beta-lactamases inactivate cephalosporins, beta-lactam/beta-lactamase inhibitor, cephamycins (e.g., cefoxitin) and aztreonam. *E. coli* can also acquire carbapenems, which gives it resistance against all beta-lactams. In the case of Klebsiella and *Enterobacter spp*. resistance also occurs through ESBL and AmpC, although it is worth remembering the emerging presence of carbapenem-resistant *Klebsiella* and *Enterobacter spp* (30).

On the other hand, Pseudomonas aeruginosa has resistance by multiple mechanisms including the production of beta-lactamases, expulsion pumps

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and porin closure, which makes antibiotics such as broad-spectrum penicillins, cephalosporins and carbapenems may be ineffective in treatment. In addition, they may develop resistance to fluoroquinolones by making mutational changes in DNA gyrase and/or topoisomerase. Resistance to aminoglycosides occurs due to the presence of aminoglycoside inactivating enzymes or methylase coding genes. The selection of appropriate antibiotic therapy is complex in infections caused by P. aeruginosa (30).

b. Methicillin-resistant *Staphylococcus aureus* (MRSA)

Newborns are likely to acquire the S. aureus through the birth canal, breastfeeding, contact with people, and the surrounding environment. The increase in MRSA colonization rates in hospitalized newborns compared to non-hospitalized newborns (31) is alarming.

After the development of beta-lactamase-resistant semi-synthetic penicillins in the 50s, different outbreaks of methicillin-resistant S. aureus were reported (3,32). Today, there has been a steady increase in blood cultures with MRSA, from 0.9% in 1990 to 13% in 2000 (33). MRSA colonization rates in newborns range from 5 to 50%, compared to MSSA which are between 18 and 81% (3).

Resistance occurs through the acquisition and expression of the mecA gene, which encodes the penicillin-binding protein 2a (PBP-2a), leading to a very low affinity for most beta-lactam antibiotics. It is also common for MRSA, especially strains associated with health care, to have increased resistance to macrolides and clindamycin through ribosomal modifications and ejection pumps. In the case of quinolones, resistance occurs due to overexpression of ejection pumps and mutations of topoisomerase IV and gyrase(32).

5. Inappropriate use impact of antibiotics in the NICU

The inappropriate use of antibiotics has health and economic consequences. Schulman et al. conducted a retrospective cohort study of 127 Neonatal Intensive Care Units (NICU) in California that included 52,061 patients (34). It showed that the Antibiotic Use Rate (AUR) varied 40-fold among NICUs (from 2.5% patient-days to 97.1% patient-days) (34). Additionally, there was no relationship between AUR and proven infection, Necrotizing Enterocolitis (NEC), volume of surgical cases, or mortality in NICU (34). From this type of studies, it can be inferred that there is a high prescription of antibiotics that lacks justification and adherence to local epidemiological information for rational use of antibiotics. Consequently, the

indiscriminate and prolonged use of antibiotics leads to undesirable effects such as alterations in the intestinal microbiota of newborns (NB), NEC, ototoxicity, hepatotoxicity, hematological anomalies, nephrotoxicity, and the need to obtain blood samples repeatedly (35,36). The manifestations of early neonatal infection are subtle, promoting empirical and early use of antibiotics to avoid delaying treatment of a true infection, exposing about 100% of the extreme preterm population to ampicillin and an aminoglycoside (37–40).

Antibiotic resistance (AR) has become a problem because the speed at which new antibiotics are developed is outpaced by the speed at which resistance emerges as it is conditioned by the appearance of enzymatic mechanisms easily shared through plasmids between bacteria. The resistance mechanisms are the result of the selective pressure exerted by antibiotics; therefore, the greater the exposure, the greater the appearance of resistance (41). The steady growth of AR will lead to 10 million people dying a year by 2050, at a global cost of $100 trillion dollars (42). Latin America is estimated to contribute 392,000 deaths a year by 2050 due to AR (42). Sepsis is a condition of increasing concern to the World Health Organization (WHO), as it is a health care priority due to its contribution to global mortality and morbidity (43,44). It is estimated that there will be an incidence of 3 million annual cases of Neonatal Sepsis (NS) and 1.2 million annual cases of Pediatric Sepsis (PS) (45). Despite the above, there is insufficient information from low- and middle-income countries to calculate the overall burden for NS and PS, therefore further research is required in this field (45). The relationship between cases of sepsis, mortality, and morbidity may be even more bleak in the context of AR, as the range of antibiotics to be used becomes increasingly narrow, leading clinical practice to a post-antibiotic era.

Countries in poverty, with poor infrastructure, and inequitable health care provision are factors that contribute to the high incidence of NS (46). In South Asia, the incidence of NS can be up to four times higher than that reported in England and the United States (47). The etiology is characteristically different in developing countries, with GNB being responsible for more than 60% of infections, with the three main agents *Klebsiella spp*, *Escherichia coli*, and *Acinetobacter spp* (47). In Brazil, a prospective 10-year surveillance study of nosocomial infections in the NICU was conducted by Couto et al., who described that 64.1% of 290 isolates of *Klebsiella pneumonia* and 19.2% of 104 isolates of *Escherichia coli* were resistant to third

generation cephalosporins (48). Staphylococcus aureus also occupies an important place in the rate of hospital-acquired neonatal infections in Africa and South Asia, while coagulase-negative *Staphylococcus* are more frequent in Latin America and the Middle East (49). Something in common among the *Staphylococcus* is the possibility of developing resistance to oxacillin and cefazolin, which would cause the germ to be denoted as methicillin resistant. The remaining strategy to treat these germs, and even more so in bacteremia, is vancomycin a glycopeptide that requires monitoring of plasma levels, dose adjustment in the presence of renal failure, and that results in nephrotoxicity with its prolonged use (21).

The overtreatment of sepsis with negative cultures, the scarcity of resistance surveillance studies in the community and in the hospital, and the difficulty of access to microbiological methods of rapid diagnosis are factors that have conditioned the high degree of resistance to first-line antibiotics (ampicillin, gentamicin, and third generation cephalosporins) (47,50,51). Other behaviors that contribute to increased resistance have been described, such as treatments that were not pathogen-oriented, failure to practice antimicrobial control, failure to treat infection and treat colonization or contaminant, and failure to stop treatment when there is evidence of cure or when infection is unlikely (52). Colombia is currently facing a challenge with Gram-negative bacteria resistant to carbapenems, as bacteria such as *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter spp* express enzymes capable of hydrolyzing carbapenems, last-line antibiotics against bacteria resistant to other beta-lactams such as cephalosporins (53). In the face of this adversity, health care costs, hospital stay, and mortality will increase.

6. Role of the Antibiogram and Antimicrobial Stewardship Programs in the NICU

It is up to the treating clinician to decide which infants to treat, what to treat with, and how long to treat (54). The intention of the Antimicrobial Stewardship Programs (ASP) is to reduce the inappropriate use of antibiotics based on 5 fundamental pillars called the “Five-Ds” (41). These include

«The overtreatment of sepsis with negative cultures, the scarcity of resistance surveillance studies in the community and in the hospital, and the difficulty of access ... »

Diagnosis, Drug (Drug), Dosage, Duration, and De-escalation. The low specificity of clinical signs, the presence of a normal physical examination in the presence of true infection, the presence of suggestive infection symptoms caused by another type of pathology, and the absence of paraclinical tests with sufficient sensitivity to exclude neonatal infection, are factors that make diagnosis difficult (55). Sometimes the microbiological growth in the cultures is not evident but the newborn persists with clinical manifestations compatible with sepsis, which is why the antibiotic treatment continues (55). It is important to consider the clinical manifestations of prematurity and the prescription of Intrapartum Prophylaxis as two conditions that the cultures are negative, and the manifestations do not correspond to a neonatal infection (55). These are the scenarios that justify the development of strategies that facilitate the clinician to make decisions regarding whether or not to start antibiotics.

Due to a low proportion of newborns receiving antibiotics have a true bacterial infection, Yang et al. in 2012 developed a tool to reduce the rate of antibiotic use in the NICU (56). Neonatal Bacterial Infections Screening Score (NBISS) is a tool that integrates maternal risk factors, clinical presentation, and laboratory parameters of patients newly admitted to the NICU (56). In total there are 25 criteria in the NBISS, distributed as follows: 5 maternal risk factors, 15 clinical criteria, and 5 laboratory parameters (Table 2).

«Sometimes the microbiological growth in the cultures is not evident but the newborn persists with clinical manifestations compatible with sepsis, which is why the antibiotic treatment continues.»

Table 2. Criteria of the Neonatal Bacterial Infections Screening Score-NBISS

Maternal risk factors	*Score
☐ Premature or prolonged rupture of membranes (>18 hours)	☐ 1
☐ Peripartum maternal fever	☐ 1
☐ Positive maternal screening for SGB	☐ 1
☐ Maternal pyuria	☐ 1
☐ Amniotic fluid with meconium or chorioamnionitis	☐ 1
Newborn clinical presentation	**Score**
☐ Respiratory rate >60 breaths per minute	☐ 1
☐ Severe chest retraction	☐ 1
☐ Nasal flaring	☐ 1
☐ Groaning/Growling	☐ 1
☐ Seizures	☐ 1
☐ Bulging fontanelle	☐ 5
☐ Ear fluid	☐ 5
☐ Erythema around umbilical cord or belly button	☐ 5
☐ Temperature >37.7 °C or <35.5 °C	☐ 1
☐ Lethargy or unconsciousness or decreased movements	☐ 5
☐ Inability to feed	☐ 5
☐ Complete inability to suck	☐ 1
☐ Cyanosis	☐ 1
☐ Reduced capillary filling	☐ 1
☐ Shock	☐ 1
Laboratory parameters	**Score**
☐ Leukocytosis or Leukopenia	☐ 1
☐ Immature/Total Neutrophils Ratio (I/T Ratio) >0.2	☐ 1
☐ C-Reactive Protein >6 mg/L	☐ 8
☐ IgM >20 mg/dl	☐ 1
☐ Need to carry out a cerebrospinal fluid study	☐ 1

*Neonatal Bacterial Infection Screening Score. A score >8, with weighted variables, can make a diagnosis of bacterial infection, helping in the decision to administer antibiotics to newborns admitted to the NICU. Adapted from: Yang, TN et al (56)..

In the investigation by Yang et al., cases defined as Bacterial Infection (BI) in newborns were established through positive blood cultures, positive urine culture, positive CSF culture, or pneumonia (56). After exclusion, 250 patients were examined (250/254), of whom 29 were diagnosed with BI. Weighting the C-Reactive Protein (CRP) with 8 points if elevated, and with 5 points to the following clinical criteria: bulging fontanel, ear canal fluid, erythema around the belly button, reduction of spontaneous movements, and inability to feed, generated a value of 0.60 for the Receptor Operating Characteristic (ROC) curve. The diagnosis of BI could be made with a weighted

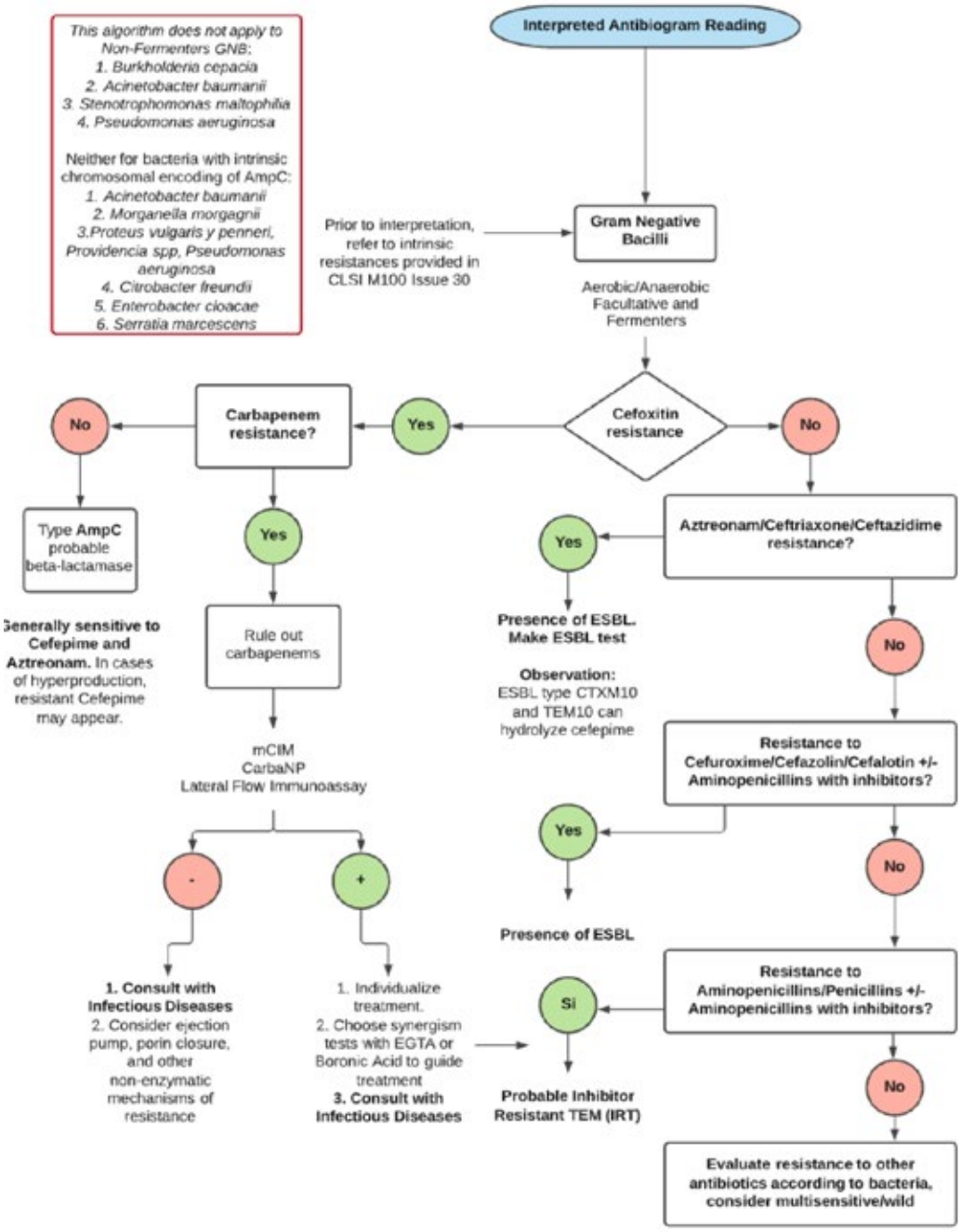
score > 8 points (56). Similarly, other strategies to detect NBs at risk of early neonatal sepsis have been developed with the aim of guiding the decision of timely initiation of antibiotic (39,57,58).

The Center for Disease Control (CDC) has been at the forefront of fighting the inappropriate use of antibiotics and preventing AR. One of the most recognized campaigns was implemented in 2002 through 12 steps to prevent AR in hospitalized patients (59). The first study evaluating adherence to the CDC's 12 steps found that the main step to which there was no adherence was "Pathogen-oriented treatment" (39% of all inappropriate therapies) (52).

In 2011, the CDC launched the Get Smart campaign (60). The objective of this was based on the five components of ASP, emphasizing that the Drug (Drug), used as empirical therapy, must be guided by local epidemiology and accumulated antibiograms. The interpreted reading of the antibiogram to make an appropriate choice of antibiotic is of great value, since identifying the pattern of resistance may avoid increasing mortality by helping to De-escalate, discontinue, or continue empirical antibiotic therapy (60). (Figure 1).

« The interpreted reading of the antibiogram to make an appropriate choice of antibiotic is of great value, since identifying the pattern...»

Figure 1. Interpretation of Antibiogram in Gram Negative Aerobic/Anaerobic Facultative Fermenters Bacilli. (E.g., Escherichia coli, Klebsiella pneumoniae)



*ESBL= Extended Spectrum Beta-lactamase, IRT= Inhibitor Resistant TEM, CLSI= Clinical and Laboratory Standards Institute. This algorithm does not apply to Non-Fermenters GNB such as Pseudomonas aeruginosa. It is important to keep in mind that there are bacteria that produce chromosomal AmpC beta-lactamases such as Acinetobacter baumannii, Morganella morgagnii, Proteus vulgaris, Enterobacter cloacae, among others. You can consult the phenotypic tests for the detection and differentiation of carbapenems in the article made by Villegas et al. (64).

** Own elaboration figure.

Culture reports are also useful to distinguish between a germ that generates a true infection (coagulase-positive Staphylococcus) and a colonizing or contaminating germ (coagulase-negative Staphylococcus). Similarly, it is essential to know the intrinsic susceptibility of the most frequently isolated germs, widely reported by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee for the Evaluation of Antimicrobial Susceptibility Testing (EUCAST) (61–63), where Klebsiella pneumoniae is described as intrinsically resistant to ampicillin, as well as Enterococcus faecium, and Enterobacter spp.

An ASP should have a team composed, ideally, of a neonatologist, an infectious disease physician, an infection prevention specialist, a bio-informatics expert, and a neonatal care nurse (55). The participation of all these professionals will depend on the availability of resources of the health center. The team has the responsibility to quantify and report metrics that they consider important to implement changes and make the ASP sustainable (Table 3.). The team should rely on institutional microbiological data to establish their empirical therapy for germs with the highest isolation frequency. It is important to consider the homogenization of practice against Neonatal Infection among clinicians in charge of decision making (55).

Table 3. Useful antimicrobial stewardship metrics for the NICU

Primary commands	Secondary Mandates	Metrics
Avoid redundant use of antibiotics	Reduce concomitant use of antibiotics with an anaerobic spectrum.	DOT with concomitant use of piperacillin/tazobactam, meropenem, or imipenem with metronidazole >1 day
Reduce broad-spectrum antibiotic use	Reduce the use of antibiotic prophylaxis for clean surgical procedures Reduce vancomycin use Reduce the use of third generation cephalosporins.	DOT with non-cephazolin-based perioperative prophylaxis for cardiac surgery
Reduce duration of antibiotic use	Avoid prolonged use of post-surgical prophylaxis. Avoid prolonged use in culture-negative sepsis	DOT with perioperative prophylaxis >48 hours Inter-quantile range of DOT duration of treatment in culture-negative sepsis.
Avoid inadequate therapy	Reduce episodes of drug-germ mismatch for LOS treatment.	Inadequate therapy DOTs per 100 LOS assessed.

*DOT (Days of Treatment); LOS (Late Onset Sepsis). Taken from: Cantey & Patel (55).

Conclusions

The existence of antibiotics has dramatically reduced mortality from bacterial infections, although their efficacy may decrease with prolonged, inappropriate use and in non-indicated scenarios due to the great threat of antibiotic resistance that bacteria can develop. The efficiency of resistance transmission by conjugation mechanisms makes even more worrisome the speed at which resistance can appear, overcoming the rate at which new antibiotics are produced.

It can be concluded that the scenario of EOS and LOS is a therapeutic challenge. This is reflected in the need to develop studies that allow the design of strategies to help clinicians in the decision-making process regarding when to initiate antimicrobial therapy in a newborn. The impact of antibiotic use, whether indicated or not, on the newborn is not negligible since it is related to fatal conditions such as NEC or renal injury.

Strict surveillance of the germs responsible for neonatal infections and resistance patterns is needed. The rational use of antibiotics based on local epidemiology should be the premise that prevails in medical practice. The training of treating physicians on microbiology and treatment-oriented should be part of continuing education. Studies are required to determine the burden of neonatal infection from antibiotic-resistant germs and to design and validate strategies that seek to promote the rational use of antibiotics such as NBISS. The implementation of an ASP should be done outside and inside the NICU, with the aim of homogenizing the medical practice of antibiotic use.

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Toxicological diagnosis in the critical patient: The challenge

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Abstract

Introduction: A high percentage of patients who survived to poison will be transferred to the Intensive Care Unit (ICU) to continue their management in relation to the severity of the poisoning, and possible complications that arise in this scenario. The clinical results will depend on several factors, such as the ingested dose, the characteristics of the substance, the time of medical attention, and the pre-existing state of health of the patient.

Objective: To review the clinical behavior of poisonings in the critically ill patient.

Recent findings: The data bases that yielded relevant bibliographical results were Web of Sciences, Scopus, PubMed, SciELO, and bibliographic references published between 2012 and 2020 were chosen.

Conclusions: The clinical behavior of poisonings in the critically ill patient is atypical. The intensivist must have an in-depth knowledge of the behavior and pathophysiology of the toxins since making a medical diagnosis on the

stage of the critically ill patient is challenging. The integration of all possible medical tools is required to achieve this in the absence of clinical history, and the implementation of early management strategies is necessary to reach physiological restoration by using a continuous evaluation approach. The severity of poisoning in the critically ill patient demands interdisciplinary management that includes assessment by Clinical Toxicology.

MeSH Keywords: Toxicology, blood poisoning, acute toxicity, critically ill, critical care.

Introduction

Poisoning continues to be a public health problem in the world. According to the World Health Organization (WHO), more than 900,000 people die annually from self-inflicted injuries, and particularly in Colombia, there are poisonings associated with agricultural activity, and accidental and environmental poisonings (1). The poisonings correspond to 1-3% of the income to the emergency department (2). The underreporting of cases is ostensibly high and often these patients present severe symptoms that require support management in the intensive or intermediate care units (2). It is calculated that the admission of patients to the ICU corresponds to 10-15% of the cases which generally present multiple organ failure and high risk of death due to the severity of poisoning, or other basic factors that worsen the clinical course of the patients (comorbidities). The toxicological diagnosis in settings outside the intensive care unit is largely based on the data obtained from the anamnesis, and on the findings of the physical examination, by associating the set of clinical signs with the possible agents, this process is also called toxidromes (3). The classification in toxidromes allows the clinician to quickly diagnose and identify the possible causative agent and apply an early implementation of therapeutic strategies that have an impact on the clinical results (4). However, there may be multiple agents poisoning scenarios or situations that may mask the typical clinical signs of toxidrome and confuse the clinician; particularly in the ICU setting where are confounding variables that hinder the correct toxicological diagnosis. Given the complexity of the clinical scenario, it is ideal to have a toxicology specialist to guide the identification of the agents involved (6). Interventions aimed at emerging physiological needs are the cornerstone of treatment, and in this clinical setting, not only detailed evaluation is required, but also constant reevaluation (5).

Epidemiology

Poisonings continue to be a public health problem in the world, even in developed countries with high-quality health care systems (1,7). The Toxic Registry of the United States reported in 2019 that most of the poisonings are attributed to analgesic medications (15.2%) of which acetaminophen corresponds to 58.2% of cases, ibuprofen to 12.9% and aspirin to 11.7%. In the second place, sedative poisonings such as benzodiazepines represented 53.1%. In the third place, there are opioid analgesics (10.9%), heroin represented 37.9% of the cases, followed by oxycodone with 12.4%, and fentanyl with 10.1%. Finally, psychoactive substances such as cocaine and methamphetamines correspond to only 6.2% and ethanol poisoning to 6.1% of all poisonings in that country in spite of the high underreporting that also occurs in this regard.

A high percentage of patients require in-water resuscitation during their care (70.2%), ventilatory support and cardiovascular support (25.5%), advanced toxin removal therapies (24.8%), and renal support therapy (43.4%) as well as ICU stay. A mortality percentage of 0.9% was reported from a total of 7.043 patients registered in the record (8). In underdeveloped countries, pesticide poisoning for agricultural use is more frequent, reaching up to 20% of fatal events, compared to 0.5% of drug fatalities in industrialized countries (9). Furthermore, in Latin America and the Caribbean, it is considered that there is underreporting of poisonings (1). Thus, The Pan American Health Organization (PAHO) reports that exposure to chemical contaminants continues to be an issue that is not given enough attention to (10). In 2017, the national incidence of poisoning was 80.6 cases per 100,000 inhabitants (11) and according to the toxic report of the National Institute of health (12), in Colombia the notification trend has been increasing. In general, the consumption of chemical substances for autolytic purposes is mainly found in young adult patients while accidental poisoning occurs mainly in older adults or children (7). The timely diagnosis, especially the early intervention guided by the symptoms of the intoxicated patient, can improve the clinical results (13).å

Toxicological syndromes (Toxidromes)

The order of toxidromes presentation goes as follows: The sedative-hypnotic is the more frequent with 10.8%, followed by the anticholinergic with 6.6%, then, the sympathomimetic with 4.7%, the opioid with 3.8%, and finally, the syndrome cholinergic corresponding to only 0.7% of cases (8).

A toxidrome is a set of clinical signs and symptoms typical of certain specific xenobiotics with similar mechanisms of action. Toxidromes are a navigation chart for the clinician, who can carry out the differential diagnosis within the multiple potentially causative toxic agents through physical examination, and also, provide a guideline for taking laboratory tests and treatment (14).

Poisonings are commonly found in critical medicine and intensive care either by accidental exposure (occupational, adverse drug reactions, accidents at home) or intentional exposure (suicide attempt or substance abuse). All patients with confirmed or suspected toxicity should be managed preventively by providing the necessary supports, identifying the causative agent, and finally, supplying the antidote if applicable (15). Some toxidromes have similar characteristics and are not fully presented as described in the literature, which can be confusing when making the diagnosis, so it must be carefully evaluated and inquired with the patient or companions (3). The description of the different types of toxidromes is presented below:

1. Anticholinergic

This is a toxidrome that occurs due to side effects of psychiatric medications or anesthesia, involuntary intoxication, or intoxication of criminal origin with drugs with anticholinergic activity. Medicines or substances with anticholinergic action act by inhibiting muscarinic receptors and consequently, inhibiting the action of acetylcholine. Muscarinic receptors are associated with the parasympathetic nervous system, which is located in different organs and systems such as the skin, eyes, heart, respiratory system, bladder, and gastrointestinal tract (3).

Pathophysiological speaking, anticholinergic agents act as competitive antagonists against acetylcholine at the level of the muscarinic receptors, produce a decrease in the activity of acetylcholine and finally, decrease the release or synthesis of it (3). The typical clinical manifestations of these anticholinergic agents are mydriasis, redness of the skin, delirium, anhidrosis, and hyperthermia; however, to carry out a systematic review on physical examination, the manifestations are divided into central and peripheral. The symptoms of central origin that appear are confusion, restlessness, apprehension, speech difficulties, agitation, hallucinations and in more serious cases, even stupor and coma (16). The peripheral type symptoms can be mydriasis, blurred vision, photophobia, tachycardia, arterial hypertension, sometimes arrhythmias such as flutter or atrial fibrillation, atrioventricular

blocks (AV blocks), supraventricular tachycardia, and even QT prolongation. At the respiratory level, there are findings of tachypnea and dryness at the nasal level. In terms of gastrointestinal symptoms, these are characterized by oral dryness, dysphagia, and ileus, the latter is identified as one of the most common complications and predictors of greater mortality and a longer stay in the ICU (17). At the urinary level, there is urinary retention, neuromuscular tremor or clonus, and in cases with greater involvement, there is presence of rhabdomyolysis. Dryness is observed in the mucous membranes, as well as in the skin, which can be better evidenced in the areas where the greatest number of sweat glands are concentrated and consequently, it leads to hyperthermia due to the inability to sweat and also thermoregulate the heat of the body.

2. Cholinergic

Acetylcholine is a neurotransmitter found throughout the nervous system, including the Central Nervous System (CNS), the autonomic ganglia (sympathetic and parasympathetic), the postganglionic system of the parasympathetic nervous system, and the motor endplate of skeletal muscle. Acetylcholine is the neurotransmitter that binds and activates the muscarinic and nicotinic receptors, and in turn, the enzyme acetylcholinesterase (AChE) regulates the activity of acetylcholine within the synaptic cleft (3).

Acetylcholine binds to the active site of AChE where the enzyme rapidly hydrolyzes acetylcholine to choline and acetyl; subsequently, these hydrolyzed products rapidly dissociate from AChE so that the enzyme is free to act on another acetylcholine molecule, but the AChE inhibitory substances like organophosphates and carbamates, prevent the inactivation of acetylcholine, generating overstimulation with acetylcholine (18).

The clinical manifestations generated by this toxidrome are affected in all systems since both muscarinic and nicotinic activated receptors lead to sympathomimetic system activation and stimulation of the neuromuscular plate junction. In view of this, hyaline rhinorrhea, salivation, bronchorrhea, bronchoconstriction, and cough, which clinically manifests wheezing and an increase in the expiratory phase, occur at the respiratory level. In the cardiovascular system, the manifestation is given by decreased activity due to bradyarrhythmias and hypotension. Additionally, at the level of the skin and the sweat glands, there is presence of tearing, blurred vision, meiosis, and diaphoresis (18). Furthermore, the cholinergic innervation in the gastrointestinal system causes an increase in the intestinal motility and relaxation

of the reflex tone of the anal sphincter; this results in salivation, increased intestinal motility, nausea and emesis, crampy abdominal pain, watery salivation, and gastrointestinal hyperactivity with symptoms such as nausea, vomiting, tenesmus, and diarrhea. The cholinergic stimulation of the detrusor muscle of the bladder causes contraction of the urinary bladder and relaxation of the muscles of the trigone and sphincter resulting in involuntary urination (18).

Seizures are frequently seen in severe cholinergic poisonings due to effects of the excess of acetylcholine in CNS. The stimulation of nicotinic receptors on the motor plate may initially lead to twitching but these may rapidly progress to flaccid paralysis. The tendency to cause seizures, as well as paralysis, puts cholinergic patients at risk of a non-convulsive epileptic state (3,14)

Organophosphate-type insecticides can produce a clinical entity called the intermediate syndrome, which is characterized by proximal paralysis of the cranial nerves, the flexor muscles of the neck, and the breathing muscles between 24 to 96 hours post-intoxication (19, 20). The mechanism by which this occurs is not well clarified; however, some studies suggest that there is a decrease in AChE and the expression of the nicotinic acetylcholine receptor (nAChR) and mRNA, in addition to increased oxidative stress and alteration of the neuromuscular plate at the postsynaptic level (18).

3. Sympathomimetic or adrenergic

Norepinephrine is the neurotransmitter that acts at the level of β1, β2, α1 and α2 adrenergic receptors, which are found in fibers that innervate the skin, eyes, heart, lungs, gastrointestinal tract, exocrine glands, and some neuronal segments in the central nervous system (CNS). The physiological response to stimulation and activation of the sympathetic nervous system produces CNS excitation (agitation, anxiety, tremors, delusions, and paranoia), tachycardia, seizures, hypertension, mydriasis, hyperpyrexia, and diaphoresis (21). In severe cases, cardiac arrhythmias may occur and may even lead to coma. The etiology of this type of toxidrome is given by abuse of substances such as cocaine, amphetamines and their derivatives (MDMA, methamphetamine), designer drugs (e.g mephentermine, mephedrone), and drugs such as ephedrine, pseudoephedrine and caffeine (21).

4. Opioids

The abuse of the prescription of opioids and the increase in illicit sales have created what is colloquially known as the opioid epidemic, and con-

sequently the increase in poisonings by this type of agent (22). Opiates are naturally narcotic derived from opium, which are isolated from the poppy plant. Some of these are semi-synthetic compounds such as morphine and codeine, and others are synthetic compounds such as hydrocodone, hydromorphone, oxycodone, methadone, and fentanyl (22).

All of these medications have potent sedative analgesic properties, but they all have different pharmacokinetic properties depending on their three main classes of opioid receptors: mu (m), kappa (k), and delta (d); or OP3, OP2, and OP1, respectively. Several of these opioids have different affinity profiles for opioid receptors, which explain the differences in clinical effects (14).

Opioid poisoning may present generalized clinical manifestations depending on the agent used, dose, method of administration, and presence of other drugs or substances of abuse. The classic toxidrome consists of myosis plus respiratory depression (hypoventilation, bradypnea), and depression of the central nervous system. There is also a decrease in intestinal motility (14), which is expressed on physical examination as a decrease or absence of bowel sounds, hypotension, and hypothermia (22).

5. Serotonergic

Some opiates such as fentanyl, meperidine, methadone, codeine, tramadol or oxycodone, selective serotonin, and norepinephrine reuptake inhibitor antidepressants, yagé, and some antiparkinsonian agents may produce serotonin syndrome, which consists of increased serotonin concentrations in the central nervous system, a neurotransmitter responsible for regulating mood, social behavior, sleep, memory and even digestion (23) The classic triads consist of neuromuscular excitation (hypertonia, tremor, spontaneous or inducible myoclonus, hyperreflexia), excitation of the autonomic nervous system (tachycardia, hyperthermia, mydriasis, diaphoresis, nausea, diarrhea) and altered state of consciousness (agitation, confusion). In some severe cases, the symptoms can include rigidity, respiratory failure, coma, and severe hyperthermia (24).

6. Sedative-hypnotic

The hypnotic sedative drugs are CNS depressants such as benzodiazepines, barbiturates, and ethanol. The chronic use of these substances can develop tolerance, and the abrupt cessation or reduction in the amount of these drugs can precipitate a life-threatening withdrawal syndrome (25). It is manifested by the deterioration of the state of consciousness with different

intensity variables (clouding, stupor, coma), miosis (with slow response to light), hypothermia, respiratory compromise (bradypnea, respiratory arrest) and cardiovascular affections (hypotension, bradycardia, cardiac arrest) (3).

7. Hallucinogen

Hallucinogens can cause a variety of physical and psychological manifestations. Among the symptoms that can occur, hallucinations, psychosis, agitation, perceptual distortions, depersonalization, derealization, muscle hyperactivity, synesthesia, seizures, hyperthermia, and mydriasis are the most common (26).

What is the clinical behavior of poisoning in the critical patient?

Patients with exogenous intoxication in the ICU do not have a well-established clinical course; furthermore, their complications are not predictable and when it comes to typifying a toxicological emergency, the uncertainties are greater concerning other pathologies treated in the ICU. The clinical history is usually not reliable, hindering the application of adequate therapies and antidotes for the patient. Thus, the relevance of recognizing potential complications early, and intervening early as well, is one of the priorities for the management of critically intoxicated patients. The most crucial action is the monitoring of clinical patterns, rather than a specific management that sometimes cannot be performed. Some poisonings may be initially asymptomatic (sustained-release drugs), and it subsequently presents deterioration of the physiological variables in a rapidly progressive manner, and it is sometimes not identified in a timely way (27). The implementation of therapies aimed at reestablishing physiology allows, on the one hand, to gain time while identifying the etiology of the condition, and on the other hand, help to minimize the morbidity and mortality associated with late management.

The clinical manifestations are varied and may be related to the patient's general health and comorbidities. These factors could mark the response to a stressor that is in this case, given by the effects of the xenobiotic, which make it difficult to characterize the population from the clinical point of view (14). There is no typical pattern expressed by intoxicated patients in critical condition, and in this sense, the intensivists must carry out an approach for toxidromes. As it was previously mentioned, the manifestations are varied and are given by effects derived from the toxic non-intervened or inadequately intervened pathophysiological consequences. In this sense, the natural course can evolve into a critical condition that includes neuro-

logical compromise, circulatory instability, and multi-organ failure leading to death. These are common effects in this group of patients regardless of the xenobiotic that caused the condition, which deserve management in the intensive care unit (28). The clinical behavior of poisonings in the critically ill patient could be grouped according to the consequences of the toxidromes reviewed in advance; thus, a patient with exogenous intoxication has a potential risk of multiple complications, including the following conditions (5,29):

a. Respiratory failure: A cholinergic toxidrome may present hypoxemic, hypercapnic, or mixed respiratory failure, characterized by sialorrhea and bronchorrhea, depressed neurological state, or muscle weakness due to motor plate compromise. A deterioration in the muscular strength necessary to generate adequate airflow finally compromises hematosis (the exchange of gases). In an opioid toxidrome, there is a significant deterioration of the sensorium, which compromises the protective capacity of the airway (2).

b. Shock state: In the case of cholinergic manifestations, the origin may be mixed, specifically; hypovolemic due to intestinal and extraintestinal losses typical of his condition, as well as a cardiogenic component given by bradycardia. Unlike opioid and hypnotic-sedative toxidrome, in which the main mechanism is distributive given the loss of sympathetic tone of the circulatory system. Furthermore, multiple xenobiotics can impair the patient's heart rhythm, that is why an electrocardiographic study is essential and mandatory in this population (2).

c. Hypertensive emergency: Target organ involvement may occur mainly over the central nervous system in anticholinergic, sympathomimetic, and serotonergic toxidromes, and it is given by an increase in the pressor response outside the range of self-regulation of blood pressure, supported by a state of psychomotor agitation. Reason why, an adequate control of its neurological condition and systemic vascular resistance are necessary for the Intensive Care Unit (2).

How to make the diagnosis in the critical patient?

Making the diagnostic approach to the intoxicated patient in the ICU raises a challenge for the intensivist since on many occasions the critically ill patient is not able to provide information that contributes to making the diagnosis of poisoning. As previously mentioned, the diagnosis depends largely on the anamnesis, a process in which it is possible to obtain information on the type of toxic ingested, the amount, the time, and the answers

to the questions: how was the contact? Where did it occur? Why did it occur? Is it the first time it occurs? Are there various substances involved? What history of illnesses does the patient have? Does he/she present use of medications, chemicals or other substances? (30). If the patient is admitted to the ICU with all the complete information collected from the emergency department, the therapeutic approach continues according to the available antidote protocols (30). However, some patients enter the ICU with unclear symptoms, with an incomplete medical history and with a diagnosis of poisoning made through suspicion, by matching the symptoms or findings that are compatible with toxidromes (2,5). In terms of toxicological testing, there exists limitation that if the samples are taken outside the window period, they can come out falsely negative (5), and this is why the toxicological diagnosis in the critically ill patient is a challenge. The following case is an example of a patient who entered the ICU under the influence of sedoanalgesia, intubated, and without information on his condition, whose toxicological process and etiology were diagnosed after receiving a thorough evaluation. (2).

Case 1

A 36-year-old male patient, with a history of epilepsy, was found on the public highway with a seizure status, he was administered with benzodiazepines and when faced with refractoriness crisis, orotracheal intubation was performed. At the moment of admission, the patient was hypertensive, mydriatic, presented tachycardia, and was under the effects of sedoanalgesia. Normal results were found when conducting a simple skull tomography. He was initially treated in the ICU with suspicion of seizure status and considering hypertension and tachycardia secondary to it. An electroencephalogram was conducted after 36 hours without seizure activity, but still with circulatory instability and irregular evolution. Toxicological tests were carried out with positive results for amphetamines and meta-amphetamines.

In this case, we can infer that intoxication was not the initial diagnosis, and given the multiple confounding factors, and even the overlapping of the base pathology and various substances consumption, the evaluation for toxidromes was challenging. The intensivist should then initially ask the critically ill patient without complete information on the condition, whether he is intoxicated or not. This question should be asked whenever we are dealing with a patient with an unclear diagnosis, with an irregular clinical

evolution, with typical clinical signs (stigmata of venipuncture, trauma), and in this sense, a permanent evaluation and re-evaluation is required. The performance of toxicological laboratory studies, images, or sometimes, when there is no toxicology laboratory, late results, or false negatives given if the samples were taken outside the window period, the diagnosis may be made by evaluating the clinical response to empirical management. The recognition of patterns is not typical in the critically ill patient, thereby the clinical and paraclinical diagnostic tools must be integrated when facing high levels of suspicion. Additionally, an adequate interpretation of the constellations of signs and symptoms must be done since toxidromes can also appear partially or mixed if several substances are involved, which may mask the findings (2). All critically ill patients require an initial and serial electrocardiographic study to determine QRS abnormalities, QT abnormalities, or classic signs of certain toxins ("digitalis cuvette", which is a decrease in the ST segment of concave shape). Table 1 summarizes some of these findings and causal agents (2).

Table 1. Electrocardiographic Findings in Poisonings

Arrhythmias	Tachyarrhythmia, bradyarrhythmia, ventricular arrhythmias
QRS ANOMALIES	Long QRS: Tricyclic antidepressants.
QT ANOMALIES	Fluoroquinolones, ondansetron, macrolides, arsenic, haloperidol, tricyclic antidepressants, trazodone, methadone, cocaine, amiodarone.
CLASSIC SIGNS	Digoxin; digitalis cuvette.

Adapted from Brent, J et al. (2)

Multiple xenobiotics can deteriorate the acid-base and electrolyte state that develop neurological manifestations and compensatory responses that demand ventilatory support (28). It is necessary to carry out an arterial gas test since it allows general practitioners to assess the severity of the poisoning, evaluate perfusion disorders, and make a specific diagnosis for some substances. The structured approach allows evaluating the primary disorder (acidosis/alkalosis; metabolic/respiratory) if there are secondary disorders, evaluation of the anion gap to rule out, or confirm poisoning. On one hand, when there is elevated AnionGap (>12mEq/L), poisoning by ASA (Acid acetylsalicylic), ethanol, and methanol, ethylene glycol is suspected. On the other hand, when the AnionGap is normal (8-12 mEq/L), poisoning by carbonic anhydrase inhibitors or ion exchange resins is suspected (5). Some laboratory tests such as lactate levels, transaminases, OsmolGap, electrolytes, serve to guide possible etiological agents. Table 2 describes the laboratory findings related to poisoning (2).

Table 2. Laboratory findings related to poisoning

Hyperlactatemia	Carbon monoxide, cyanide, or methanol.
Sodium levels	SIADH*; Selective serotonin reuptake inhibitors (SSRIs) Diabetes insipidus; Lithium
Arterial gases: HYperchloremic acidosis	Topiramate
Potassium levels hypokalemia	Methylxanthines
Nitrogen containing compounds	Ethylene glycol, acetaminophen, cocaine. Rhabdomyolysis (antipsychotics, neuroleptic malignant syndrome, sympathomimetics, opioids.)
Transaminases coagulation times	Acetaminophen. Hepatotoxins (plants, essential oils, herbal supplements, over-the-counter and prescription medications, halogenated hydrocarbons.
OsmolGAP	Alcohol poisoning

*SIADH (Syndrome of inappropriate antidiuretic hormone secretion)

Adapted from: Brent, J et al 2. Kent R et al13 Zarbock A et al. (33).

Toxicological tests can be done in blood or urine, and it is preferable to carry out the first tests with quantitative levels. It should always be evaluated whether they alter the course of the disease or change its behavior since it has been described that the performance of tests only modifies treatment in 15% of cases (2,14). It is considered that they should be performed within 1-5 days of the onset of symptoms; however, this varies according to the substance (30,31). Table 3 summarizes the main toxics and their window to obtain a reliable result.

Table 3. Window time for toxic detection.

Substance	Detection window time	Commentary
Amphetamines	2 days.	False positives.
Barbiturates	< 2 days. 1-week phenobarbital.	
Benzodiazepines	2-7 days* variable.	Does not detect lorazepam, alprazolam, new.
Cocaine	2 days.	Detects benzoylecgonine metabolite.
Ethanol	< 1 day	
Marijuana. Tetrahydrocannabinol THC	2-5 days. > chronic use.	
Opioids	2-3 days.	Synthetics often do not detect. Separate methadone test.

Adapted from de Kent R et al13 Zarbock A et al. (33)

Currently, there is the availability of panels that sense 40-100 substances; nonetheless, those that are analyzed are 80% of poisoning cases. In the ICU patient, the taking of toxicological samples will depend largely on availability and the speed with which the results are received, which would both change the behavior and are ultimately not routinary.30. Its taking will then be linked to the clinical context at the time the patient takes his initial picture, and to the need of clarification in the diagnosis and the implementation of advanced care measures, or to cases of illegal situations in which documentation of the toxic is required for legal reasons. 2,5,31. The practical approach to the intoxicated patient in the ICU is in the flowchart (Figure 1).

Figure 1. Flowchart.

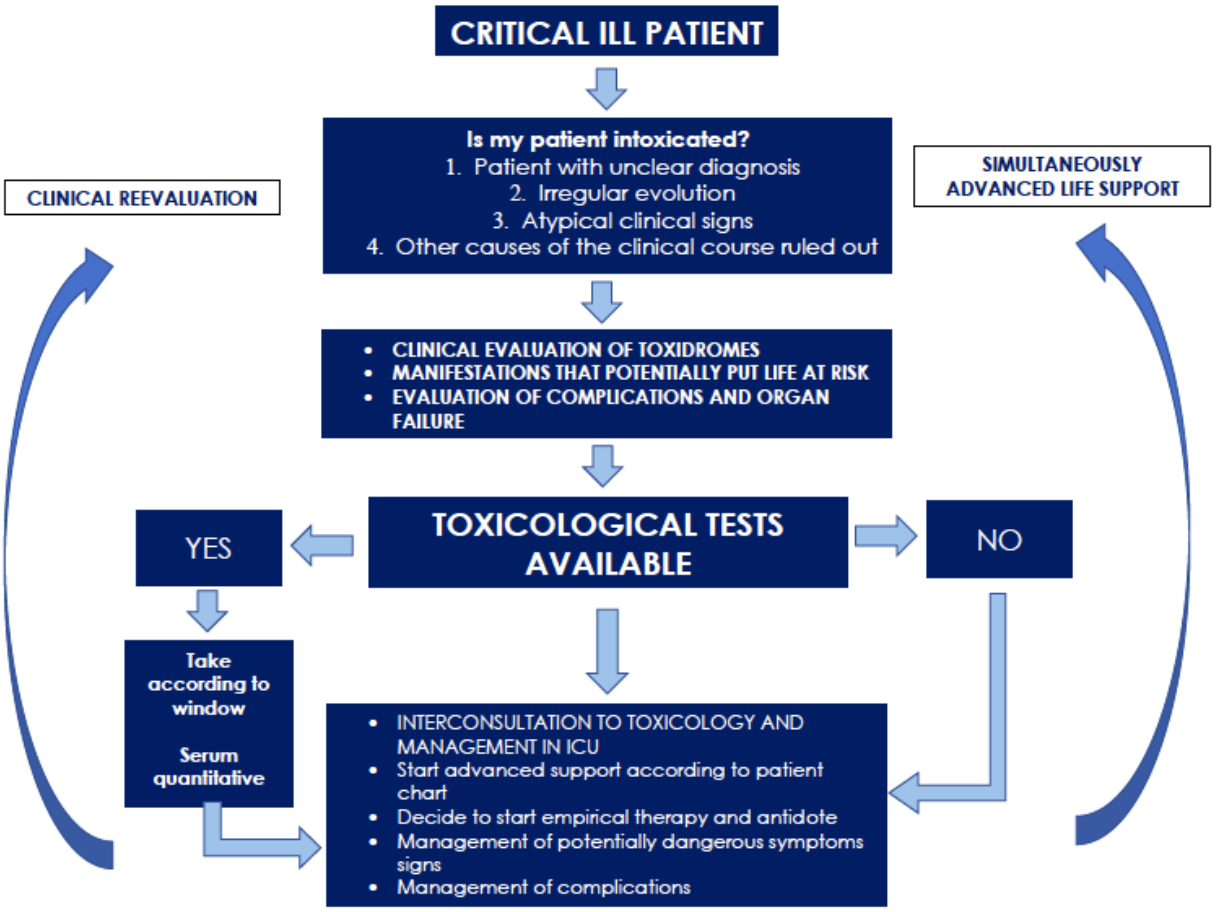

Image realized by the authors, based on references: Brent, J. et al. (2); Rasimas J, et al. (5); Thompson TM et al. (14)

Finally, images have limited the diagnostic value in this clinical setting. An x-ray can be done to evaluate for iron and lead poisoning, an abdominal and pelvic tomography can be conducted to evaluate caustic poisoning,

packaged medications, and foreign bodies (criminal behaviors), and a simple skull tomography can be implemented for making alternative diagnoses in terms of chain inhibitor poisoning transporter of electrons that produce heart attacks in the area of the basal ganglia. But, in general terms, they are not a priority (5).

What therapeutic interventions are indicated in the ICU?

The treatment of poisoning depends on the agent involved, the general measures that include the ABCD within the protocol of the intoxicated patient, and specific antidotes are described in the current guidelines. Gastric lavage is usually not indicated, and a single dose of activated charcoal can be administered if the intake is recent (<1 hour) depending on the type of poisoning and whether or not there are contraindications (30).

The implementation of early support therapies has a positive impact on both in-hospital stay, as well as in costs of care and mortality (5). It is considered essential to carry out an orderly approach to the patient taking into account the maintenance of the airway, oxygen therapy and permanent observation of the respiratory muscles' activity, and to perform early orotracheal intubation if the respiratory failure is detected. The circulation refers to the phenomenon of hypotension and arrhythmias that were mentioned in the clinical manifestations and that are susceptible to intervention, either with vasoactive support or with pacemaker implants urgently, it depends on the case of the patient (2). Table 4 summarizes the main toxics with their available antidotes.

Table 4. Main antidotes for the management of the most common poisonings.

Antidote	Indication
N- acetylcysteine	Acetaminophen
Atropine	Cholinesterase inhibitors
Absolute alcohol 96% or vials of brandy 29% for oral use	Methanol, ethylene glycol, or sodium fluoroacetate
Antivenoms	Snakebite (PROBIOL freeze-dried anticoral serum, multipurpose anticoral serum, polyvalent antifungal serum) and alacram (BIOCLON lyophilized antialacran serum)
Methylene blue	Symptomatic methemoglobin or ≥30%
Prussian blue	Radioactive thallium or cesium poisoning
Sodium bicarbonate	Tricyclic antidepressants
Deferoxamine	Iron poisoning
Dimercaprol (BAL)	Arsenic
DMSA (Succimer)	Lead, arsenic and mercury salts
Fag Shards	Colchicine
Physostigmine	Severe anticholinergic syndrome
Flumazenil	Respiratory depression by benzodiazepines
Glucagon	Beta-blockers
Calcium gluconate	Calcium channel blocker poisoning
Naloxone	Opioid respiratory depression
Amyl nitrite	Cyanide
Thiamine	Prevention or treatment of Wernicke-Korsakoff encephalopathy in alcoholics
Protamine	Reverse anticoagulant effect of unfractionated heparin
Pralidoxime	Nicotinic and muscarinic syndrome secondary to cholinesterase inhibitor poisoning
Vitamin k	Warfarin or superwarfarins

Adapted from Thompson TM et al. (14); Flanagan RJ et al. (41); Peña LM et al. (42)

Patients with acute kidney injury secondary to shock, or for poisoning may require renal replacement therapy (32-36). Dialysis is recommended in alcohol poisoning with severe metabolic concentration, serum methanol, and ethylene glycol concentrations greater than 50 mg per deciliter (methanol, 16 mmol per liter; ethylene glycol, 8 mmol per liter), if there is a deterioration of vital signs despite management, visual disturbances (associated with methanol poisoning,) or acute kidney injury (37). Intermittent hemodi-

alysis removes toxic alcohols more quickly than continuous renal replacement therapy. Depending on the redistribution of alcohol, the metabolites or both may require repeated dialysis (38).

Extracorporeal toxic agent removal therapy represents a treatment modality that promotes the elimination of exogenous toxins and temporarily supports or replaces vital organ function. The various principles that govern the elimination of the toxic through this therapy (diffusion, convection, adsorption, and centrifugation) and how the components can be adjusted to maximize the elimination have been discussed, these are aspects that the intensivist must take into account when implementing this therapeutic tool (39). Indications suggest that there is an exposure to the toxin that causes serious morbidity and mortality, the toxicity cannot be treated with an antidote. Thus, the implementation of endogenous toxic clearance of less than 4ml / min/kg, or volume of distribution <1-2 L / kg must be conducted.

A document was recently published by the International Society of Nephrology (39), which indicates a diagnostic algorithm based on the characteristics of the toxin for therapeutic decision-making. According to the percentage of protein binding of the toxin at the current concentrations during the evaluation, it is indicated that if the percentage of protein binding is greater than 95%, the use of plasma exchange therapies (plasmapheresis) is favorable, and if the binding percentage is 80%, hemoperfusion therapies are preferred. When the molecular weight is 15,000 Da, the therapy of choice is high-flow hemodialysis, if it is 15,000-25,000 Da, the recommended option is hemofiltration, if it is 25,000-50,000 Da, continuous hemodialysis or hemoperfusion are advised, and in a molecular weight greater than 50,000 Da, plasmapheresis is suggested. Recommendations are made for conducting extracorporeal therapy in cases of poisoning caused by barbiturates, lithium, methanol, metformin, salicylates, thallium, and valproate. Besides, it is recommended to apply neutral ions for treating poisoning by phenytoin, poisoning by acetaminophen and carbamazepine, and poisoning by tricyclic antidepressants and digoxin (40).

What complications are the most frequent?

The main complications can be triggered by intoxication or due to exacerbation of the patient's underlying pathologies. Respiratory failure, aspiration pneumonia, shock, multiple organ dysfunction that include liver failure and acute kidney injury requiring advanced therapy, cardiorespiratory arrest, and neurological sequelae are complications that lead to ICU stay or death.

In view of the aforementioned, the prognosis will not depend solely on the type of poisoning, but rather on the consequences derived from it and its management (2,5).

Conclusions

A percentage of patients who survive to poisoning will be transferred to the Intensive Care Unit to continue their management in relation to the severity of the poisoning and possible complications that arise in this scenario. The clinical results will depend to a great extent on numerous factors, such as the ingested dose, the characteristics of the substance, the time of medical attention, and the pre-existing state of health of the patient. The clinical behavior of poisonings in the critically ill patient has a neurological and circulatory predominance, supported by acid-base, electrolyte, and heart rhythm compromise secondary to different xenobiotics that require monitoring and advanced management in the ICU. The intensivist must have an in-depth understanding of toxic behavior and pathophysiology since making a toxicological diagnosis is challenging. The integration of all possible tools is required to achieve this in the absence of medical history, and the implementation of early management strategies to restore physiology using a continuous evaluation approach is necessary. The severity of the intoxication in the critically ill patient demands interdisciplinary management that counts in addition to the evaluation of clinical toxicology.

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Use of the cardiac ultrasound at emergency room for general physicians

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Abstract

Ultrasonography at the Emergency Room (ER) becomes a useful tool for emergency doctors, especially when they need to attend to diseases that require faster treatment. This is an ideal non-invasive exam which is cheap and can be implemented in real time to obtain instantly the missing information. The quick recognition of the causes of the cardiac instability will lead to better results for conditions such as cardio-pulmonary resuscitation (CPR). The aim of this article is to show the usefulness of cardiac ultrasonography and to briefly teach general practitioners at ER about it.

Key words:

Emergency medicine, Echocardiography, Cardiovascular diseases, Clinical skill, Transthoracic echocardiography.

Introduction

The cardiac ultrasonography is a basic imaging exam, which is useful for evaluating cardiac patients who come to the ER. This exam is advantageous for showing the condition of the hemodynamic status or the presence of any cardiac lesions. All of them could be performed in real time to get information for the prognosis and follow-up procedures. In Colombia, it is believed that the ultrasonography is an exclusive tool for the radiologist or other specialists; therefore, general practitioners have been unable to interpret it. However, in the ER of developed countries, this tool has surpassed

the stethoscope and also played a crucial role in medical student education.

From 2015 to 2018 the prevalence of risk factors of suffering from cardiovascular disease was 49.2% in adults over 20 years old. Then, the highest cause of death by cardiovascular disease was the Coronary Artery Disease with an incidence of 42.1%, followed by the Stroke with 17.0%, and Heart Failure with 9.6%. Among the Hispanics in the United States, Cardiovascular Disease was the first cause of death in nearly 30% of males and females (1).

In Colombia, according to the National Institute of Health, heart diseases were the first cause of mortality until 2015, with ischemic coronary disease as the first cause with 41.8%. 2 Besides, at least 10% of the thoracic trauma is associated with the cardiac trauma3, and its mortality is estimated around 76%.4 The reason for this variability of the rate could be that the patients coming to ER cannot know the specific state of the damage to the heart.

The importance of knowing the myocardial function could help the physician to make a correct management, and reduce the high mortality presented due to conditions such as pericardial tamponade, dysfunction of the cardiac wall motion, and hypovolemia. Furthermore, the European Resuscitation Council (ERC) guidelines for resuscitation 2005, recommended the intermittent application of cardiac evaluation by ultrasonography during the cardiopulmonary arrest (CPA). The recognition of the causes of CPA and the quick resolution actions of these lead to a better result of return of spontaneous circulation (5,6). For all hemodynamically critical patients, transthoracic echocardiogram (TTE) can identify the causes of shock, and those key findings often change the treatment to be followed (7,8).

To conduct TTE screening, it is not necessary for general doctors to have the same training as sonographers (9). General practitioners need to complete a couple of required techniques and receive eye training to make a decision to treat the patients. In developed countries, the medical students already have close contact with the ultrasonography. However, in this country where the health system is poor, they do not have enough budget and opportunity to receive the training.

In this review, we will describe the minimal technique to get proper images of TTE and the way to analyze obtained data to make proper decisions in ER.

1. Clinical Application

a. Thoracic Trauma

The objective of using ultrasonography is to determine the presence of an active bleeding in pericardial space after trauma. It will be seen as pericardial effusion, but such effusion does not imply to be cardiac tamponade. The cardiac tamponade is a status in which the abnormality of blood or

other fluid circulation is determined. The pericardial effusion that follows the rupture of the myocardial muscle will disturb the dilatation of the wall motion, resulting in the deterioration of vital signs.

b. Cardio-Pulmonary Arrest (CPA)

The ultrasonography in CPA is so useful that it can change the prognosis of victims. It can show the situation of the heart in real time, evaluate intravascular volume, and find the etiology of the CPA. Based on all this data, the life support team can effectuate a better job.

c. Hypovolemic Shock

Cardiac ultrasonography can help the case of unknown hypotension on critical scenes, mainly by evaluating if the hypotension is caused by cardiogenic shock or not. In addition, it can repeatedly evaluate the levels of severity.

d. Chest Pain

Doctors at ER often consult patients with chest pain. Here, the performance of ultrasonography is not only to evaluate the heart function since it has an essential role in detecting the presence of high mortality diseases such as aortic dissection or pulmonary embolism. If doctors do not find any severe etiologies, they will start to perform routine cardiac screening in detail.

2. Technique

Doctors should choose TTE as a part of the cardiac evaluation at ER as well as knowing medical history and conducting other physical and laboratory exams. There are three points to check: global wall motion, the size of the cardiac chambers and the presence of pericardial effusion. TTE has many windows, but the basic ones are the long axis (LAX), short axis (SAX), four chamber (4Ch), and subxiphoid acoustic window. Finally, it is also necessary for doctors to understand the anatomical position of the heart.

a. Long axis view (LAX)

This window is between the 3rd to 5th intercostal space with the left parasternal line. The marker of the transducer will be pointed at 10 o'clock or the right shoulder. Examiners can observe the right ventricle, the aorta, and the left atrium and ventricle. At the same time, they can evaluate the wall motion, chamber sizes and presence of pericardial effusion. The chambers can be measured with the measuring tool in the machine, but they must not spend a long time in an emergency. In this view, the left ventricle should not be bigger than the right ventricle. (Figure 1.)

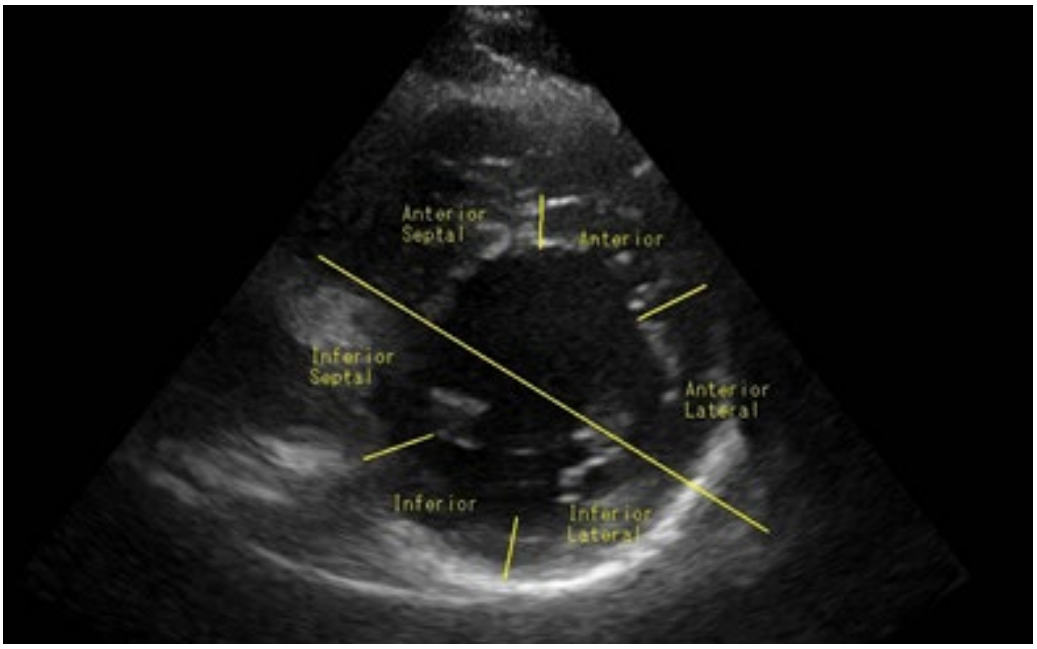

Figure 1. The anatomial position of the heart, showed in short axis view.

b. Short axis view (SAX)

The second window is SAX. From LAX, the examiners rotate the probe at 90 degrees in a clockwise direction at the same parasternal point. From this view, they can see both the ventricles at the transverse plane. The left ventricle appears as a circle while the right ventricle seems as a crescent moon. The key point of this view is to evaluate at the level of papillary muscles since examiners can get a clear image for the evaluation of wall motion. Based on that, it is important to comprehend the orientation of the heart, and to know which wall portion is damaged. (Figure 2. And Figure 3.)

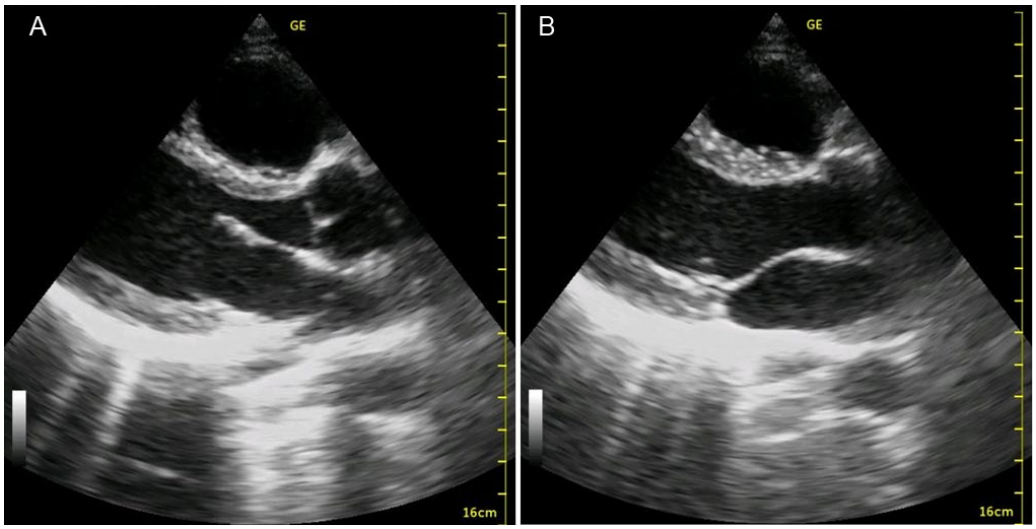

Figure 2: Long axis view. Dyastolic (A) and Systolic (B) period.

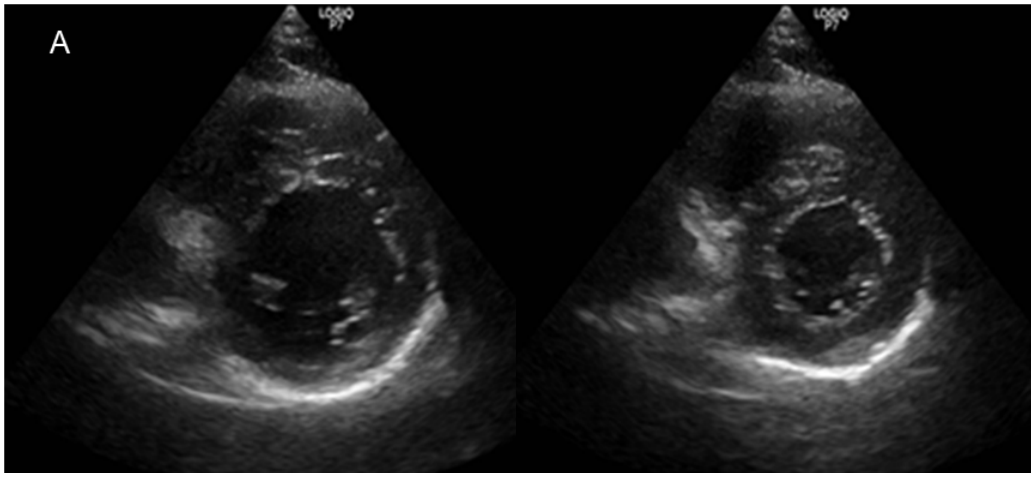

Figure 3: Short axis view. Dyastolic (A) and Systolic (B) period.

The evaluation points are the same as in LAX: the wall motion, chamber sizes, and presence of pericardial effusion.

c. Apical 4 chamber

The third window is the apical 4 chamber. Here, the examiners will approach the probe from the sixth intercostal space in the left axillary line. The image shows the apex at the top of the screen, including the whole heart with its 4 chambers. The ventricles appear on the upper side of the screen and the left heart will be seen at the right side of the screen. The crucial structure in this view is the moderator band inside the right ventricle. It is important to confirm the laterality of the heart too. The main points are the same as LAX and SAX: wall motion, chamber sizes and presence of pericardial effusion. In suspected cases of intraventricular thrombus, this view can identify it especially at apical portion. (Figure 4.)

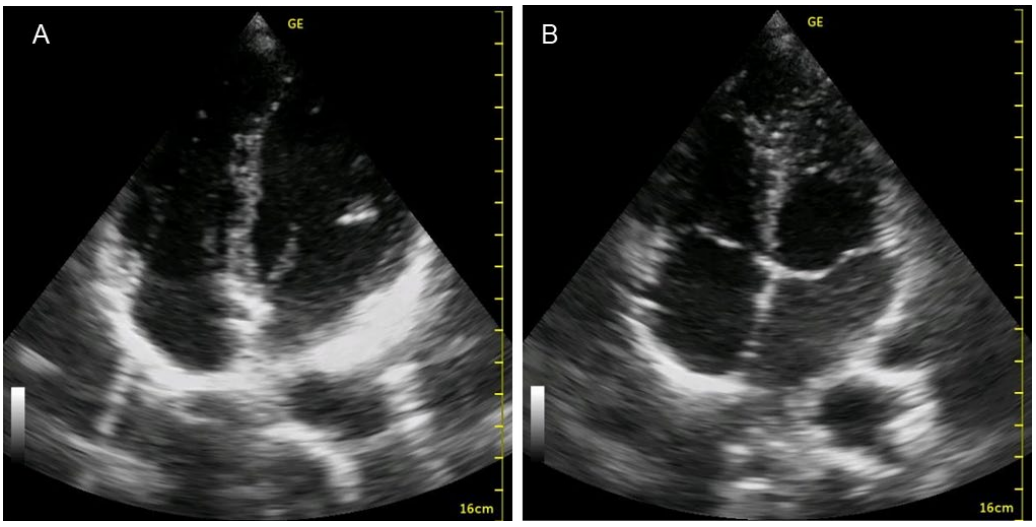

Figure 4: Apical four chamber view. Dyastolic (A) and Systolic (B) period.

d. Subxiphoid view

Ultrasonography at cardiac arrest situations can improve the result in the return of spontaneous circulation (ROSC). Using that, the life support provider has more available information for making a decision (10). Although the approach should be performed from the epigastric window, the evaluation during cardiac arrest is not easy. When using subxiphoid view, examiners do not interfere with the chest space for chest compression. This view is the same as the four chambers' and the evaluation points are the same as in the other views: wall motion, chamber sizes and presence of pericardial effusion. Needless to say, to rule out the treatable causes of CPA is the most important aspect.

e. Inferior Vena Cava (IVC)

The approach to the IVC is made through the same window of subxiphoid view. Examiners should rotate the probe to the sagittal plane. If there is no appearance of IVC, they tilt the probe to the left side in many cases. In this window, it is important to show the right atrium continuing to the IVC. The examiners ask the patient to inspire deeply to obtain a proper image. The IVC view is useful to indirectly evaluate the volume condition. If IVC collapses to the half in the beginning, it means a normal intravascular volume. If the IVC collapses completely or maintains expanded during the inspiration, it could alert a volume alteration and the physician should reconsider the fluid therapy. (Figure 5.)

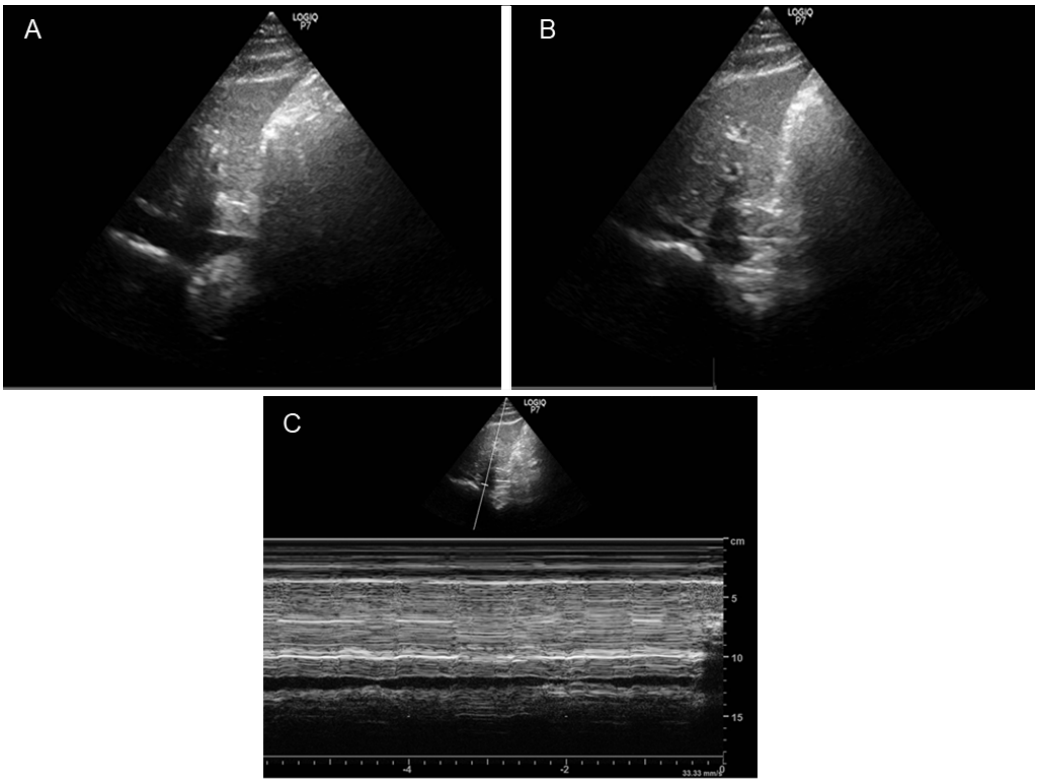

Figure 5: Inferior Cava Vein (IVC). Breath out (A) and Inspired (B), and measured by M mode (C).

Key sentence

Ultrasonography is a modern and indispensable tool for physicians who work in the emergency room or manage critical care patients.

TTE should be used to determine etiologies and evaluate the prognosis in any critical care scenes.

The emergency ultrasonography should be performed for future medical treatments for a short time. Physicians never take a long time to perform ultrasonography for the diagnosis.

General practitioners at ER need to complete a couple of required techniques of TTE and receive eye training for hours. The TTE is not for specialists but general practitioners.

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Fiebre de malta: reporte de caso

Malta fever: Clinical case

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Abstract

Introduction: Malta fever (brucellosis) is a zoonotic infection produced by intracellular gram-negative coccobacilli, which is transmitted by the consumption of infected unpasteurized animal products, skin contact or mucous membranes with infected animal tissues and fluids, and inhalation of infected aerosolized particles.

Case: A 34-year-old man living in a rural area, who works in livestock, was admitted to the emergency department for presenting a clinical picture of 15 days of evolution of unquantified febrile peaks associated with symptoms such as chills, asthenia, adynamia and myalgia. The diagnosis of infection with Brucella Abortus was given through clinical-pathological correlation.

Conclusion: This pathology is more frequent in adult males. Serological studies (antibodies, agglutination and immunochromatographic assay) prove to have the highest sensitivity and diagnostic specificity in the clinical picture. The treatment is given with medication that acts on intracellular acidic environment (tetracyclines, aminoglycosides, fluoroquinolones), this in order to control the disease, and prevent complications and relapses.

Keywords: Brucellosis; Malta Fever; Brucella; Fever (MeSH)

Introducción

Brucellosis, also known as 'undulant fever', 'Mediterranean fever' or 'Malta fever' is a zoonotic infection produced by bacteria of the genus Brucella, which is found within the Alphaproteobacterial family (1).

Members of the genus Brucella are small, facultative intracellular, non-encapsulated, non-sporulated, and non-motile, aerobic gram-negative coccobacilli. Classically 6 species were recognized within the genus Brucella: B. melitensis, B. abortus, B. suis, B. canis, B. ovis and B. neotomae, where its name was seen according to the host (cattle, sheep, goats, camels, pigs or other animals) (2). Only the first three are harmful to humans and present their own pathogenicity that is transmitted to humans through the intake or ingestion of food products from infected animals (such as unpasteurized dairy products) or by contact with tissues or fluids (1) (2).

Currently, Brucellosis is considered a reemerging disease and represents a public health problem in many developing countries (3) (13), since the prevalence of brucellosis has increased due to increasing international tourism and migration (1).

Different endemic areas have been found for this infectious disease, in which are including countries in the Mediterranean basin, the Middle East, Central Asia, China, the Indian subcontinent, Sub-Saharan Africa, and parts of Mexico and Central and South America. (4) Worldwide, approximately 500,000 cases are reported annually, and an estimated 2.4 billion people are at risk (2), (5), (12).

The objective of the following paper is to present the clinical case of a patient with Malta fever (Brucellosis) treated at the San Rafael hospital of Tunja.

Clinical case.

34-year-old man living in the rural area of Sotaquirá (Boyacá). He was admitted to the emergency service of a second-level health center, due to a clinical picture of 15 days of evolution of unquantified fever peaks with associated symptoms like chills, asthenia, adynamia and myalgia; he reported having consumed amoxicillin 500 mg every 8 hours, chlorpheniramine 4 mg each 8 hours and ascorbic acid 500 mg per day for 7 days without showing improvement.

He reported important work history of contact with cattle and their fluids without adequate biosecurity elements. The admission vital signs were temperature 37.9 °C, heart rate 117 beats per minute, blood pressure of 110/70 mmHg, respiratory rate of 20 breaths per minute, it was highlight-

ing tachycardia and fever, in the general physical examination did not reveal alterations other than the described.

Due to the patient's work history and clinical picture, it was decided to perform paraclinical (Table 1), where the seroagglutination tests confirmed the diagnosis of brucellosis; due to this result, management with doxycycline 100 mg orally every 12 hours and rifampicin 300 mg orally every 8 hours for 6 weeks were given, with which an improvement was obtained, and the patient was indicated to be follow-up on an outpatient basis.

Tabla 1. Laboratorios de ingreso.

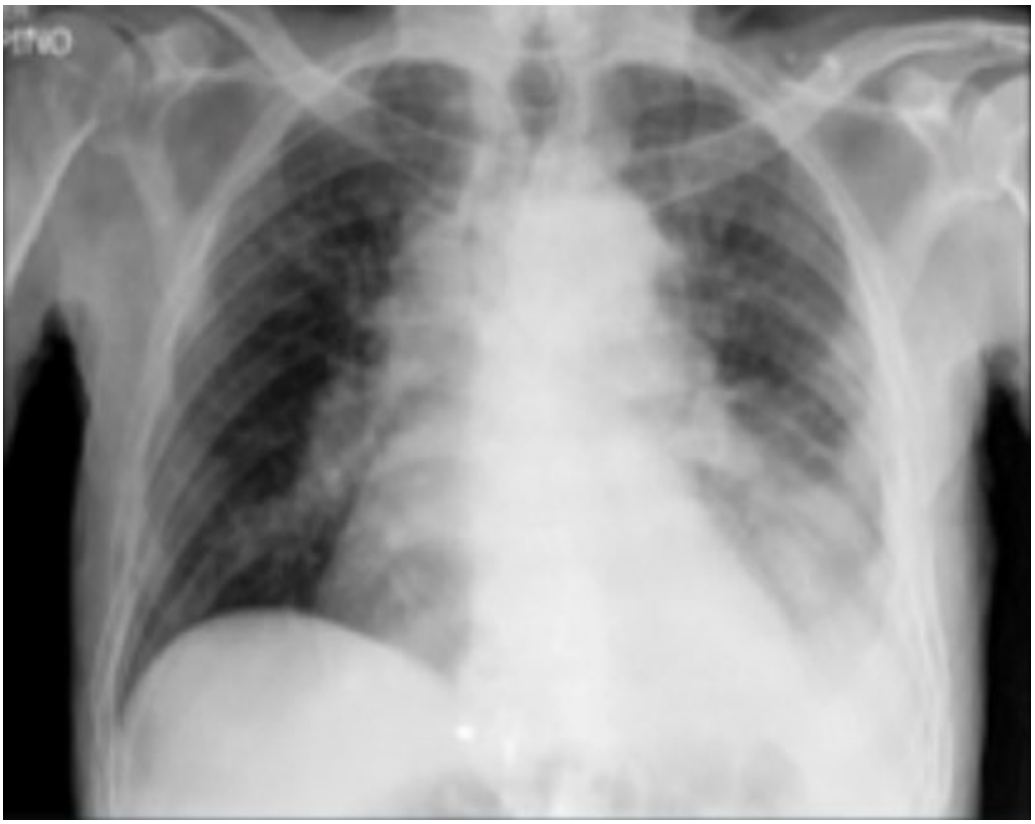
Tabla 1. Admission laboratories.

Laboratories	Results	Reference
Leukocytes	98600/mm3	4500 a 11000/mm3
Neutrophils	46.8%	40,0 a 65,0 %
Lymphocytes	41,40%	30,0 a 40,0%
Monocytes	11,60%	3,0 a 10,0%
Platelets	226000/mm3	150 a 350000/mm3
Hemoglobin	14,5 gr/dl	14,50 a 16,50 g/dl
C Reactive Protein	50,8 mg/l	0.5-10 mg/l
Blood Culture	Negative at 48 hours	Negative
Urine Culture	Negative at 48 hours	Negative
TGP/ALT	104 U/L	Hasta 42 UI/L
TGO/AST	70 U/L	Hasta 37 UI/L
Hepatitis B Surface antigen	Negative	Negative
Hepatitis C Antibodies	Negative	Negative
WIDAL Reaction	Negative	Negative
Salmonella Typhi O	Non-reactive	Non-reactive
Salmonella Typhi H	Negative	Negative
Salmonella Paratyphi A	Negative	Negative
Salmonella Paratyphi B	Negative	Negative
Weil Felix Reaction	Negative	Negative
Total anti-Brucella antibodies (rose bengal method)	100 UI/ml positive	Less than 25 UI/ml
Huddleson Reaction (*Brucella* Abortus)	Reactive (1/320)	Non-reactive

Once the treatment was completed, the patient was evaluated again for outpatient consultation by the infectious disease service who considered that the dual treatment (doxycycline and rifampicin) was suitable, however, the patient persisted with positive serology for infection by Brucella (Huddleson reaction -Brucella Abortus- positive plate agglutination technique), for which the handling indicated was modified as follows: ciprofloxacin 500mg tablet every 12 hours for 20 days, doxycycline 100 mg every 12 hours for 20 days and control laboratories.

The patient was admitted again to the emergency department 10 months after the last admission, due to similar clinical picture to the one previously presented, this time associated with myalgias and arthralgias, the laboratories showed a slight increase in transaminases, the abdominal ultrasound showed hepatosplenomegaly and chest X-ray did not show alterations, the trachea in a central position, at the level of the lung area no condensation or data suggestive of abnormal atelectasis were observed, cardiac silhouette within normal limits, free cardio and costophrenic angles, bone mineralization within normal parameters (figure 1).

Figure 1. Chest X-ray.



In view of the results obtained in the ultrasound and chest X-ray, it was decided to hospitalize the patient indicating management for suspected relapse by Brucella with Doxycycline 100mg every 12 hours plus gentamicin 240 mg intravenously per day. The patient completed 6 days of in-hospital antimicrobial management; he was presenting improvement in symptoms so discharge with outpatient follow-up was indicated.

Discusión

In Latin America, Mexico has the highest annual incidence of Brucellosis cases. In South America, Peru and Argentina have the highest incidences of 34.9 and 8.4 annual cases per million inhabitants. In Colombia, the incidence is 1.85 annual cases per million inhabitants. The disease in non-endemic areas is of occupational origin and the most affected population are male adults (6).

Table 2 lists the main clinical manifestations and most frequent laboratory findings and their prevalence (14).

Table 2. Clinical and paraclinical characteristics of Malta fever.

Table 2. Clinical and paraclinical characteristics of Malta fever (1).	
Clinical manifestation	**Prevalence (%)**
Fever	76%
Discomfort	68%
Night sweats	72%
Arthralgias	80%
Hepatomegaly	50%
Splenomegaly	29%
Paraclinical Findings	**Prevalence (%)**
Alanine aminotransferase increase	33%
Anemia	27%
Leukopenia	9%
leukocytosis	8%
Relative lymphocytosis	24%
Thrombocytopenia	12%
Pancytopenia	<1%

It is important to consider that for patients with fever of unknown origin, the panel of antifebrile antigens should be performed to rule out other infectious pathologies, within which blood cultures that have a low sensitivity

for brucellosis (15 to 60%) (1) can be performed; due to, for this case it was preferred to perform serological tests that allow the detection of antibodies against lipopolysaccharide or other antigens of bacteria such as the IgM and IgG ELISA (sensitivity 94%, specificity 97%), Rose Bengal agglutination test (sensitivity 87%, specificity 100%) and the immunochromatographic lateral flow assay (sensitivity 92%, specificity 97%) (1, 6, 7), which were positive in the case presented.

The goal of the treatment is to control the disease, prevent complications, relapses, and sequels (8) (15), which is why combined antibiotics with activity in acidic intracellular environments are included, at high doses with prolonged duration as it decreases the risk of relapse (7). Within the management regimens for the general population, doxycycline can be combined with an aminoglycoside (streptomycin or gentamicin) or the combination of doxycycline with rifampicin for 6 weeks; the first combination is being more effective and with lower risk of relapse (8). In cases of relapse or therapeutic failure, fluoroquinolones should be added (9).

For pregnant women the treatment is still uncertain, since tetracyclines are contraindicated (10), however in pregnancies of less than 36 weeks, it can be given management with trimethoprim sulfamethoxazole with rifampicin for six weeks, and in case of more than 36 weeks it is preferred to give rifampicin monotherapy until delivery due to the risk of neonatal kernicterus with the use of trimethoprim sulfamethoxazole. After delivery, it is given management with combination therapy as in non-pregnant adults (11).

Between 5 to 15% of patients after treatment may relapse, it even may occur up to 12 months later (1), among the factors that can predict relapse are temperature ≥38.3 ° C, symptoms duration <10 days before treatment and positive blood cultures at the beginning of the study. Causes of relapse include inadequate antibiotic regimen, inadequate duration of antibiotic therapy, lack of adherence, or localized outbreak of infection (1) (7).

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Fístula colovesical secundaria a diverticulitis complicada: tratamiento laparoscópico - Reporte de caso

Colovesical fistula secondary to complicated diverticulitis, laparoscopic treatment – A case report

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ABSTRACT

Introduction: The colovesical fistula is a junction between the urinary bladder and the large intestine. It occurs in 2% of patients with diverticular disease of the colon and generates symptoms such as pneumaturia and fecaluria associated with recurrent urinary tract infections. The patients are diagnosed by imaging studies and their treatment is usually surgical.

Objective: To report the laparoscopic treatment administered to a patient that presented a case of colovesical fistula secondary to severe diverticulitis.

Case report: The case of a 69-year-old male patient with a medical record of diverticular disease, who presented recurrent urinary tract infection, fecaluria, and pneumaturia is presented. The cystoscopy procedure showed no signs of anal fistula, and the abdominopelvic tomography showed sig-

nals of inflammations and colovesical fistula associated with complicated diverticulitis. During the laparoscopic procedure, a pericolic abscess was found without eviden´ce of anal fistula. Drainage and suture of the colon and omentum interposition were performed without presenting intestinal resection. The patient had an adequate postoperative recovery and was discharged on the sixth day. The aim of this surgical treatment is focused on the control of medical complications caused by diverticulitis, in this case, colovesical fistula.

Conclusions: This procedure is minimally invasive, and it is associated with a faster functional recovery since it does not present the morbidity of a colon resection or colostomy.

Keywords: Intestinal fistula, diverticulum, abdominal abscess, laparoscopy.

Introduction

The colovesical fistula (CVF) is a pathological communication between the bladder and the large intestine, caused mainly by diverticular disease of the sigmoid colon (80%) which the probability of developing CVF in the presence of diverticular disease ranges from 1-4% of cases (1); followed by colon cancer (15%) and other less frequent causes such as Crohn's disease (5%), radiotherapy complications, bladder cancer and iatrogenic lesions (1,2).

This communication favors the passage of intestinal content towards the bladder and vice versa, that is why there are multiple clinical manifestations such as pneumaturia (71% - 90%) and fecaluria (51% - 76%), which are considered signs pathognomonic of this pathology (3). The presence of fecal matter in the urinary tract provides the environment for the appearance of recurrent urinary tract infections, which is why the presence of irritative urinary symptoms is frequent in these patients (66%); In addition, other manifestations such as abdominal pain (71%), hematuria (30%) and localized peritonitis (14%) (2) may occur. The clinical manifestations of this entity vary from one patient to another, becoming as severe as an urosepsis, more frequent in older adults (3).

The diagnosis of CVF is generally made by the clinical chart of the patient, but verification through imaging tests is important to confirm it, locate the area where the fistula is located, and rule out the presence of other possible complications (4). There are multiple imaging studies that allow the identification of CVFs, among these the gold standard is computed tomography (CT) with double contrast, since it has a high sensitivity (> 90%) to

identify the lesion and allows the visualization of adjacent structures (4 ,5). The treatment of CVF is mainly surgical, generally by laparotomy the correction of the fistula and resection of the compromised intestinal segment is performed (5).

The objective of this case report is to present the clinical history and the atypical evolution of a colovesical fistula secondary to complicated diverticulitis grade IIb, managed by laparoscopic technique, without resection of the affected intestinal segment.

Case report

69-year-old male patient with a clinical history of diverticular disease, arterial hypertension (AH) and benign prostatic hyperplasia (BPH). Admission to the emergency department due to a one-week clinical chart characterized by pain in the hypogastrium associated with dysuria, pollakiuria, tenesmus vesical, and non-quantified fever. At the admission physical examination, a bladder balloon was founded despite positive urination, admission paraclinics with altered renal function, albuminuria, hematuria, bacteriuria, and positive urine culture for multi sensitive Escherichia coli (E. Coli) and initial diagnostic impression of a complicated urinary tract infection, for which a bladder catheterization was performed and started antibiotic therapy.

During in-hospital management he presented an episode of fecaluria and pneumaturia, suggestive of CVF, a transurethral cystoscopy was performed in which no fistulous tracts were evident. At the lack of aetiology, a double contrast abdominopelvic Computed Tomography (CT) was performed, inflammatory findings with air inside evidenced the presence of a colovesical fistula associated with complicated diverticular disease (Figure 1). The patient was assessed by general surgery who considered the clinical chart and imaging findings that he required surgical treatment with closure of the fistulous orifice.

Figure 1. Abdominopelvic computed tomography: sagittal cut where diverticulum is evidenced at the colonic level, good pericolic abscess (White arrow), with air bubble inside it (Yellow arrow).

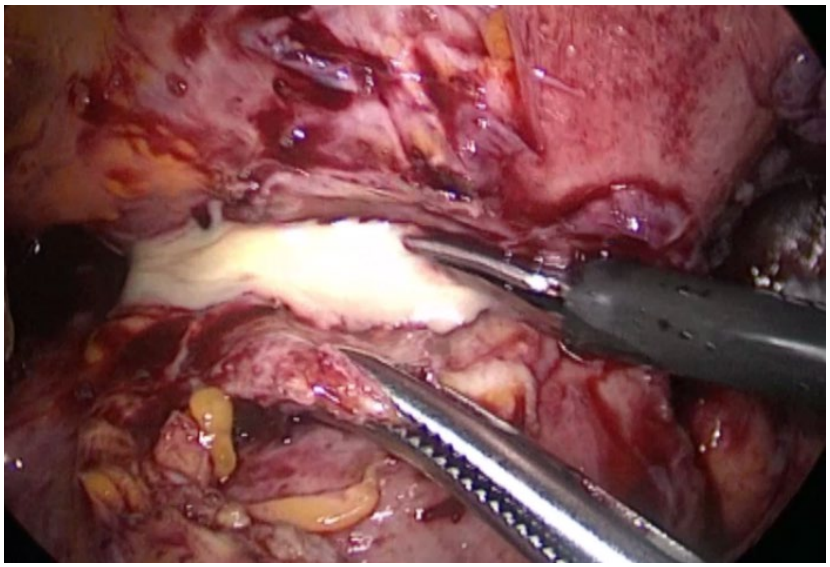

Figura 2. Fotografía intraoperatoria:
Drenaje de absceso pericólico entre el colon sigmoides y la vejiga.

The laparoscopic procedure was performed under general anesthesia. Presence of inflammatory changes with phlegmon-like of the sigmoid colon towards the pelvis. By meticulous dissection, it is possible to separate the antimesenteric border of the sigmoid colon from the posterior aspect of the bladder, identifying in this place a purulent collection between the bladder and the colon (Figure 2).

The abscess is drained, establishing the post-operative diagnosis of a pericolic abscess with colovesical fistula (Figure 3).

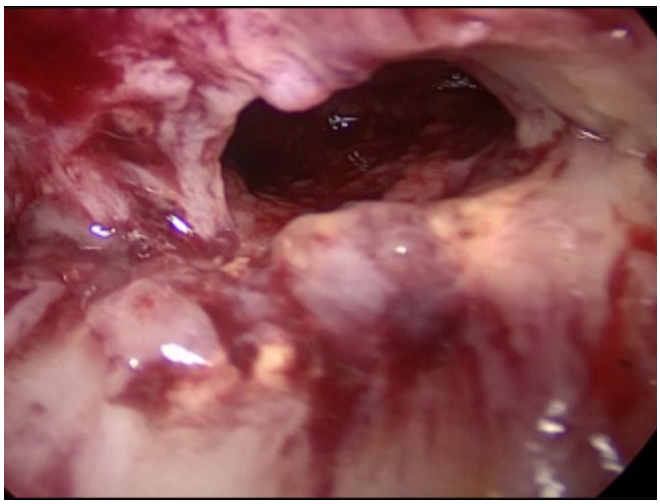

Figura 3.Fotografía intraoperatoria:
Cavidad de absceso posterior a drenaje.

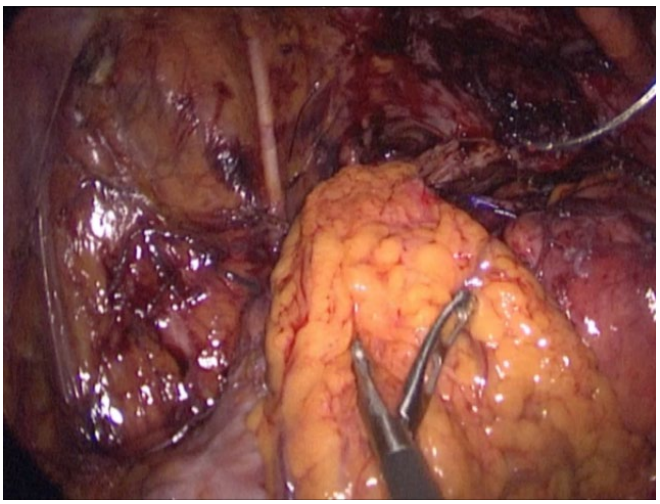

Figura 4. Fotografía intraoperatoria: Interposición con sutura de parche de Epiplón entre el colon sigmoides y la vejiga

Closure of the sigmoid defect was performed, without sigmoidectomy. Interposition of the omentum between the bladder and the anterior aspect of the rectum, fixing it with silk stitches to the perirectal tissue (Figure 4).

Drain is left in the pelvic fossa. (Figure 5) Permanent bladder catheter.

Figura 5. Fotografía intraoperatoria: Colocación de dren en cavidad abdominopélvica.

Satisfactory evolution post-operative. Clear and scarce drainage. Tube diuresis in adequate quantity and appearance. He was discharged with no symptoms six days after the procedure. 24-month follow-up and the patient remains asymptomatic, he denies new episodes of urinary infection.

Discussion

CVF is an abnormal communication between the intestine and the bladder which in 80% of cases is secondary to complicated diverticulitis, being more frequent in elderly patients, with a 3:1 ratio in men (6), which agrees with our patient.

In this case, we present a patient with a clinical history of diverticular disease that presents the usual symptoms of CVF, due to pneumaturia and fecaluria associated with irritative urinary symptoms. These symptoms are considered pathognomonic of this complication and are experienced by more than 75% of patients with CVF, so it is possible to make a clinical diagnosis (7-9).

In the presence of pathognomonic symptoms that suggest the diagnosis of CVF, it is necessary to use additional diagnostic tests to confirm the existence of the fistula, clarify the etiology, observe adjacent structures, and determine the therapeutic strategy (9). Among the most widely used studies

is the CT with oral and intravenous contrast as a first-line examination, it has a sensitivity of 92% to 100%, the findings described in the literature are the presence of air in the bladder, thickening of the bladder and intestinal wall, presence of colonic diverticula and the presence of a paravesical mass of soft tissue with air inside it (4,8,9).

Magnetic resonance imaging (MRI) has a sensitivity of 100%, it can detail the morphology of the fistula and its anatomical location (10); However, it is not performed routinely in our environment since it is an expensive and not very accessible study. The most widely used endoscopic examination is cystoscopy, a useful tool to detect bladder alterations, but its sensitivity in this case is only 35% to 60%, in which it can be directly visualized the orifice of the fistula or suggestive findings such as the edema, erythema or ulceration of the bladder wall. (4, 8,10). For this case, cystoscopy was used in the first instance, in which no suggestive findings of CVF were found, but, due to the patient's symptoms, it was decided to perform a tomography where the fistulous tract was found.

The management of CVF is divided into conservative and surgical. Conservative treatment consists of intestinal rest with total parenteral nutrition, antibiotic therapy, steroids, and drainage of the urethral catheter. This approach is considered feasible in patients with a short life expectancy, poor general condition, or who are not suitable for major surgery; However, it has been associated with a higher risk of sepsis, that is why the indication in general population is to carry out surgical management (6,8).

Regarding surgical treatment, it consists of resection and anastomosis of the affected intestinal segment and closure of the bladder (5,9,11). Traditionally it has been carried out through Laparotomy; Nevertheless, a new approach in this management is laparoscopic surgery with which greater benefits have been found. Gilshtein et al, showed a lower morbidity rate with laparoscopic surgery (11.8%) versus laparotomy (50%), being this result statistically significant (p:0.027); In addition, a seven-fold higher odds ratio (OR) of presenting complications in the surgical wound was found for the laparotomy group (p: 0.023) (12). Likewise, a shorter hospital stay has been

«This approach is considered feasible in patients with a short life expectancy, poor general condition, or who are not suitable for major surgery...»

«It is important to highlight that there is a probability of conversion to open surgery when undergoing laparoscopy in 5-40% of cases...

found in patients with diverticular disease undergoing laparoscopy compared to patients undergoing open surgery (SMD: -7.65, 95% CI (-10.96, -4.32), p: 0.000) (13,14).

It is important to highlight that there is a probability of conversion to open surgery when undergoing laparoscopy in 5-40% of cases, especially in patients with certain specific conditions, such as the location of the fistula in the posterior wall of the bladder, a history of previous abdominal operations and difficulty in seeing the CVF in the pelvis (14,15).

Considering that this patient did not have any comorbidity or risk factors for conversion to open surgery, it was decided to perform a minimally invasive procedure. During the surgical procedure, the fistulous orifice was not evidenced, which does not rule out the diagnosis of CVF, on the contrary it is an example of adequate preoperative management, which allowed natural epithelialization and closure of it, leaving therefore the pericolic abscess that did not have natural exit route, for which its drainage was essential. In the same way, due to intraoperative findings closure of the sigmoid defect is performed, without sigmoidectomy, with the interposition of the omentum between the bladder and the anterior face of the rectum, offering a preserving management of the organ, thus avoiding prolongation of the operative time and higher related morbidities with it.

There is currently no significant evidence to suggest a gold standard for the management of CVF. Therefore, it is important to individualize the patient to choose the best therapy (16). To define safety and efficacy, multicenter studies with the highest level of evidence should be carried out, which allows evaluating the variables that can predict a better or worse outcome and considering a safe, effective, and reproducible process.

Conclusion

CVF is a complication that occurs in 2% of patients with colon diverticular disease, especially in elderly people. The clinical history of this pathology is characteristic, and it can be confirmed with images. Regarding to treatment, taking into account the limited number of studies, the laparoscopic approach can be considered first line in patients with low risk of conversion to open surgery, since it is associated with a faster functional recovery and

a lower rate complications. In this case, it was decided not to carry out the sigmoidectomy, offering a preserving management of the organ, thus avoiding prolongation of the operative time and greater morbidities related to it. The maneuver of interposition of the omentum between the bladder and the colon, suturing it as a patch, offers security of the isolation of these two viscera.

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Metástasis pulmonar y pleural en cáncer de pene, una patología infrecuente.

Pulmonary and pleural metastasis in penile cancer, an uncommon pathology

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Abstract

Introduction: Carcinoma of the penis is a rare tumor in our environment, constituting less than 1% of deaths in men and it is defined as the proliferative disordered process of squamous epithelial cells of the penis.

Objective: The objective of the following manuscript is to present the case of a patient who developed cancer of the penis with metastasis to the lung.

Clinical case: An 85-year-old patient was admitted due to a 24-hour clinical picture consisting of hematuria associated with non-productive cough, low back pain, asthenia and adynamia. He had a history of squamous cell carcinoma of the penis, he was identified as a heavy smoker until two years ago and presented chronic exposure to wood smoke. On the physical examination, the patient evidenced a regular general state, respiratory sounds that suggested left hypoventilation, absence of penis due to his clinical history and outflow of hematuric urine through bladder catheter, ganglia in the inguinal region, edema in the lower limbs with formation of flictenas on the dorsal zone of the feet. Imaging studies confirmed the presence of mass in a pulmonary region together with pathological fractures

at the thoracic level, thus, palliative care was provided, and the patient was discharged from the hospital.

Conclusions: Penile cancer is a low prevalence worldwide pathology. Approximately 95% of these cancers are squamous cell carcinomas, which can easily spread locally through lymphatic or vascular channels; nonetheless, its metastatic disease development is rare and mainly affects organs such as the liver, bone, and brain. However, few cases of metastasis to the dorsal spine, heart, retroperitoneum, breast tissue, lung, and skin have been reported.

Keywords: Cancer of the penis; metastasis; lung; lymphatic squamous cell carcinoma.

Introduction.

Carcinoma of the penis is an infrequent tumor in our environment, constituting less than 1% of deaths in men (1, 2). According to a study conducted by the Universidad del Valle in 2004, in Colombia, this pathology has an incidence rate of 1.11-2 per 100,000 inhabitants and ranks worldwide as a country with low incidence of this disease; Similar findings were shown in a study in the city of Pasto between 2008 - 2012 where an incidence of 1.8% per 100,000 man-years was found (3).

This pathology generally is presented as a proliferative and disorderly process of the squamous epithelial cells of the penis. It is usually originated in the epithelium of the inner portion of the foreskin and glans. More than 95% of penile malignancies are squamous cell carcinomas (4).

Among the most relevant associated complications are metastasis, considering the biological point of view, its dissemination is carried out by an embolization mechanism and not by penetration, with initial extension through the lymphatic route to the inguinal nodes, after to the iliac chains and finally, distant metastasis is developed in less than 10% of cases (4). It should be noted that lung metastasis of primary origin in the penis are very rare in the population and even more taking into account the low metastatic level of this pathology after its surgical treatment. The treatment by partial or total penectomy is usually effective with few local recurrences. However, at the time of surgery, there may be micro-metastasis at the lymph node level that will subsequently influence the appearance of locoregional and distant recurrences (5, 6).

The objective of the following manuscript is to present the case of a patient who presented penile cancer with metastasis to lung.

Clinical Case.

An 85-year-old patient was admitted for a consisting 24-hour clinical chart of hematuria associated with non-productive cough, low back pain, asthenia and adynamia. He had a history of focally keratinizing squamous large cell carcinoma, ulcerated of usual moderately differentiated type, unifocal glans with invasion to corpus spongiosum, albuginea, caverns, penile urethra and vascular and perineural invasion, diagnosed two years ago so he required partial penectomy, he was identified as heavy smoker until two years ago and presented a chronic exposure to wood smoke.

At the admission physical examination his vital signs were blood pressure of 130/75 mmHg, heart rate 93 bpm, respiratory rate 20 rpm, temperature 36.5°, oxygen saturation 87 with inspired fraction of 21% oxygen. General regular condition, afebrile, hydrated, alert, without signs of respiratory distress, rhythmic heart sounds without murmurs, respiratory sounds suggestive of left hypoventilation, absence of penis due to clinical history and outflow of hematuria urine through bladder catheter, ganglia in the inguinal region, edema in lower limbs with formation of blisters on the dorsal face of the feet. The admission paraclinical tests showed slightly elevated C-reactive protein, the rest of the studies were within normal parameters (Table 1).

Tabla 1. Paraclínicos

Laboratorio	Resultado	Valor de referencia
Pleural fluid volume	200 cc	5 a 15 ml
Color and appearance	Amarillo turbio	
Leukocytes	862*mm^3	
PMN	40%	Hasta 10%
MN	60%	Hasta 30%
Red blood count	127000*mm^3	
pH	7	
Density	1005	
Glucose	28.70 mg/dl	60% del plasma
Proteins	3.69 g/dl	1 a 2 g/dl
Lactate dehydrogenase.	267 U/L	Hasta 250 U/L
Time of prothrombin	17.80 seg	10-14 seg
INR	1.33	
Blood count: Leukocytes	9.479 uL	4-10 x 10 3/uL
Hemoglobin	13.3 g/dL	11 – 15 g/dL
Neutrophils	76.5 % (7.240 u/L)	50 – 70%
Lymphocytes	15.1 % (1.430 u/L)	20 – 40%
Platelets	243 x 10 3/uL	150 – 450 x 10 3/uL
BUN	12 mg/dL	5 – 23 mg/dL
Creatinine	0.56 mg/dL	0 – 1,17 mg/dL
Potassium	3.71 mEq/L	3.7- 5.5 mEq/L
Sodium	137.5 mEq/L	136 – 145 mEq/L
Highly Sensitive Reactive C Protein	8.36 mg/dL	0 – 0,5 mg/dL
Prostate- specific antigen	4.77 ng/mL	1,4 -4,4 ng/mL
PCR RT SARS CoV-2	Negativo.	

Chest X-ray showed transparency with diffuse consolidated alveolar radio opacity in the middle and lower field of the left hemithorax, and right basal hilum with inflammatory appearance together with effacement (pleural effusion) in the left costophrenic angle; diffuse reticular interstitial infiltrates with chronic appearance, free right costophrenic breast, the left one was effaced. Diffuse osteo-degenerative changes (Figure 1)

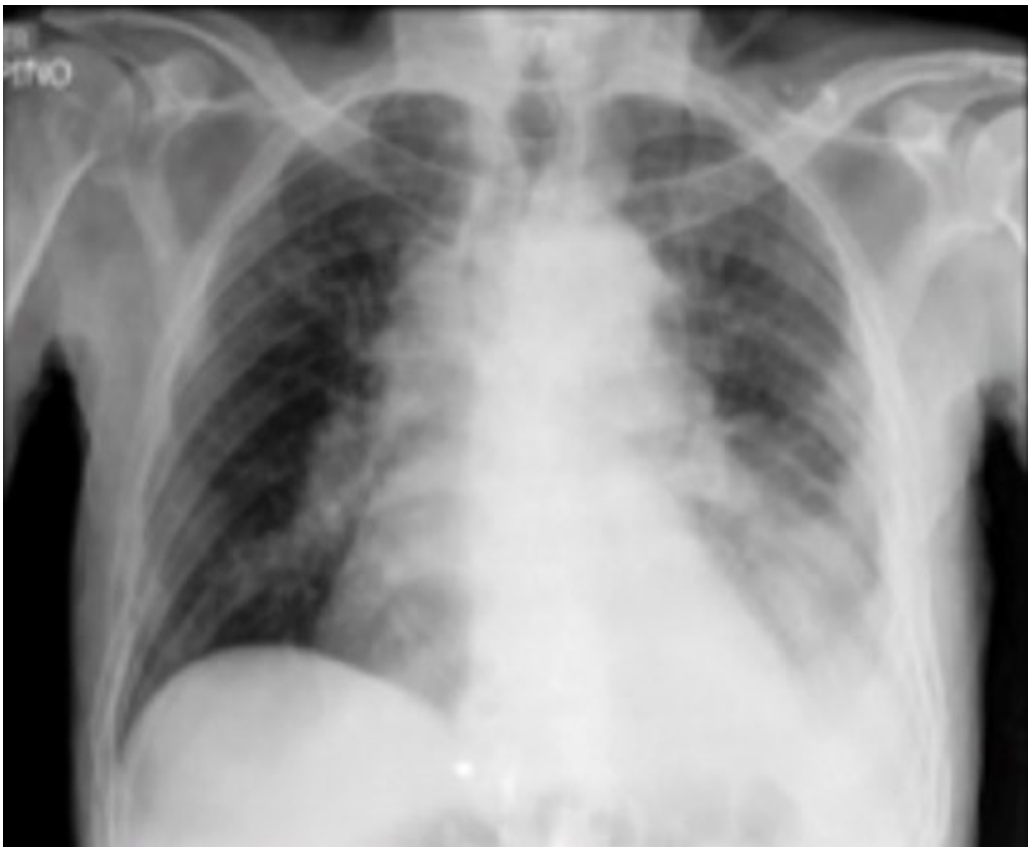

Figura 1. Radiografía de tórax PA.

Given these findings, it was decided to rule out possible SARS-CoV-2 infection, antibiotic treatment was indicated given the first suspicion of community-acquired pneumonia and a computerized axial tomography was requested that reported mediastinal, cervical and axillary lymphadenopathies of apparent metastatic origin, bilateral pulmonary nodules of neoplastic appearance, signs associated with chronic interstitial lung diseases, bulky left pleural effusion, passive atelectasis in the left lower lobe and fracture of apparent pathological origin of the vertebral body of T5 (Figure 2).

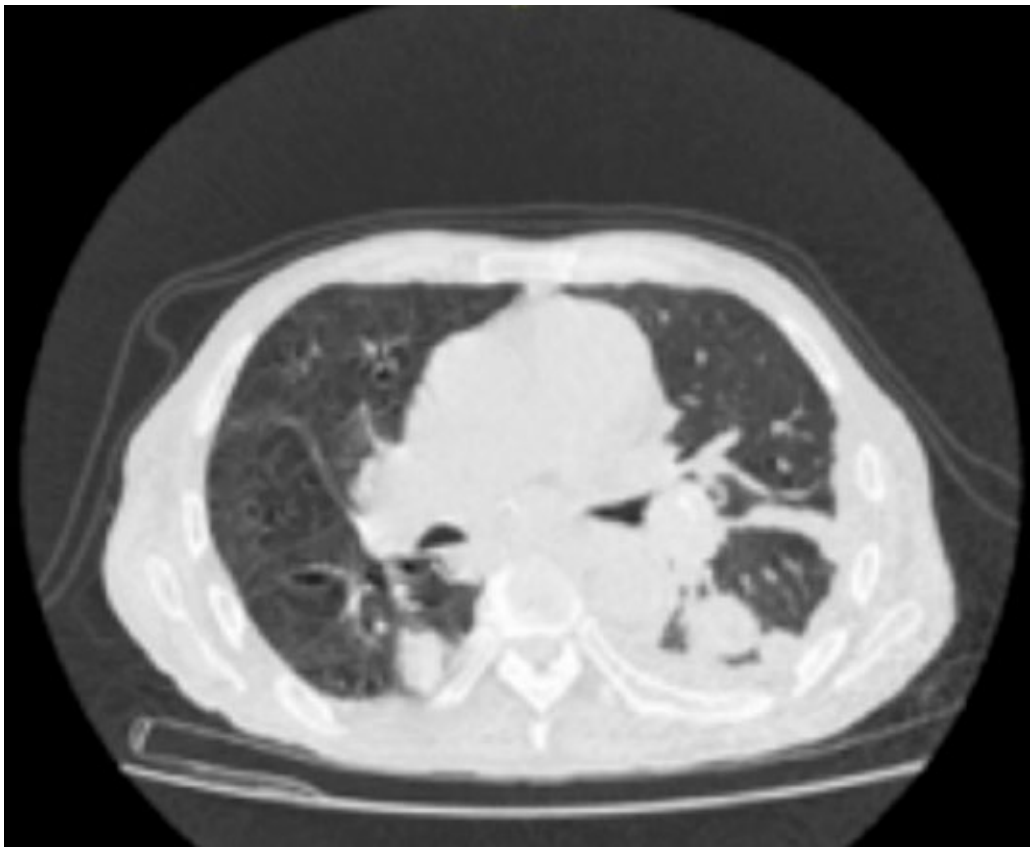

Figura 2. Tomografía axial computada de tórax.

By report of CT of the chest and clinical history it is decided to suspend antibiotic treatment and request drainage and study of pleural fluid with evidence of mononuclear exudate, negative fluid culture, so it is considered pleural effusion secondary to metastatic process. A report of PCR RT SARS CoV-2 Negative is received from the National Institute of Health, so it is decided to discharge with palliative management given the poor short-term prognosis and clinical condition.

Discussion.

In underdeveloped countries of South America, Southeast Asia, and African the incidence of penile cancer is much higher compared to the incidence in developed countries (with a maximum of 10-30% of malignant diseases in men) (5, 7, 9). In Europe and North America its incidence is approximately 1.0 new cases per 100,000 inhabitants. In countries like Germany, 195 mortality cases with an average age of 70 years were recorded for 2018 (8). As for the risk factors associated with the presentation of this pathology, phimosis and chronic irritative processes are found in relation to inadequate hygiene (9). Additionally, it is common in regions with high

prevalence of human papillomavirus, which may explain or be related to the variation in incidence (10), which also depends on race and ethnicity.

The age of onset of this pathology is between the sixth and seventh decade of life (11), however, in this case it was presented at 85 years of age. The existence of the delay in diagnosis since the appearance of the lesion and the first diagnostic consultation is striking (9). When reviewing the patient's old medical history, approximately 10 months previously he began with pruritus and subsequently the presence of penile lesion. The most frequent reason for consultation is the penile lesion (78%), which can be papillary and exophytic of warty growth or a painless, flat, and ulcerated lesion, with erythema, induration, bleeding and secondary infection. The tumor can be seen in the glans (48-52%), foreskin (21%), glans and foreskin (9%) or in preputial sulcus (6-26%) (12).

Its confirmation is made by biopsy, the usual histopathological diagnosis is squamous cell carcinoma in its different forms, from superficial, ulcerovegetative and infiltrating, constituting 95% of cases and the remaining 5% corresponds to papillary carcinoma (13).

The initial route of spread occurs through the lymphatic vessels of the foreskin to the nodes of the inguinal region initially superficial and subsequently deep, as the glans and urethra drain into the deep external inguinal nodes. The metastasis by the hematogenous route occur in less than 10% of patients, where it mainly affects organs such as the liver and bone (13– 15) and to a lesser extent organ such as the spinal cord, brain, retroperitoneum, skin and lung (16 – 22).

In general, when hematogenous dissemination occurs through the venous route, it generates peripheral lung lesions and is usually asymptomatic, although patients with lesions in the central parahilar location are due to a hematogenous spread through the bronchial arteries (23). It is important to note that the export of 0.1% of tumor cells to the peripheral circulation is required to generate metastasis (24).

The initial management is the complete resection of the primary tumor by penectomy in search of the total removal of the tumor, verifying through microscopy negative resection margins (13). Local recurrence (2-6%) is rare but may occur occasionally leading to the need for a second intervention. The metastatic process is developed initially in the inguinal nodes, then the iliac chains and finally the distant metastasis, for this reason when making the diagnosis of cancer and finding palpable inguinal adenopathies, a broad-

spectrum antibiotic scheme is necessary for six weeks before indicating any management or biopsy in the region (25), however, other studies propose percutaneous biopsy of adenopathies to confirm the presence of metastatic spread. In case of finding metastasis, it is indicated to perform bilateral inguinal lymphadenectomy (9), and subsequently follow up on patients due to in 17% of the cases, micrometastases may occur that finally leads to a torpid evolution of the pathology.

In the underdeveloped population it is difficult to carry out a complete, full, and adequate follow-up of the patients after surgical management given the low resources and the high rate of abandonment of the consultation, compared to the developed countries where the follow-up is carried out according to what the literature establishes, making it difficult to assess the evolution and establish a statistic on the rate of progression, this was what happened to the patient of this case.

Conclusions.

Penile cancer is a low prevalence worldwide pathology. Approximately 95% of these cancers are squamous cell carcinomas, which can easily spread locally through lymphatic or vascular channels; despite this, the probability of metastatic disease is rare, and mainly affects organs such as the liver, bone, and brain; however, few cases of metastasis to the dorsal spine, heart, retroperitoneum, breast, lung, and skin have been reported.

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