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Microbiological characteristics of infections in a group of colombian patients with oncological diagnosis, 2014 – 2016

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Abstract

Objective: We aimed to describe the microbiological characteristics of infections in patients from an oncological center during 2.014-2.016.

Methods: In this cross-sectional descriptive study, a total of 7.837 cultures corresponding to 1.216 patients were included. Microbiological and sociodemographic data were taken from cancer diagnosed patients admitted to Oncólogos de Occidente S.A. in Pereira, Armenia, Manizales and Cartago from January 2.014 to December 2.016. The bacterial resistance profiles were defined according to the CLSI guideline. Culture foci were blood, urine, tissue biopsies, skin and soft tissues, mucous membranes and feces.

Results: The culture-positive rate was 27,94%. Amongst 2.190 isolates, *Escherichia coli* (22,42%) was the most frequent, followed by *Klebsiella pneumonia* (21,27%), *Pseudomona aeruginosa* (13,83%) and *Staphylococcus aureus* (5,11%). The most common mechanisms of antimicrobial resistance in Gram-negatives were Extended-Spectrum β-Lactamase (45,45%) and AmpC-type β-lactamases (37,71%).

Discussion: Up to nearly one-third of our participants' cultures were positive and a vast majority were gram-negatives, provided with ESBLs or AmpCs which in oncological patients it is a catastrophic outcome. We recommend to establish antibiotic dispensing policies thus achieving a microbiological risk control and improve the epidemiological surveillance. Empirical use of beta-lactams with extended spectrum or cephalosporins of 1 to 3 generation is not recommended due to the high resistance found.

Key words: Neoplasms; nosocomial infection; microbial drug resistance; cancer care facilities; antibiotics.

Características microbiológicas de infecciones en un grupo de colombianos con diagnóstico oncológico, 2014 – 2016

Resumen

Objetivo: Describir las características microbiológicas de las infecciones en pacientes de un centro oncológico durante 2.014-2.016

Métodos: Estudio descriptivo, transversal. Incluyó 7.837 cultivos de 1.216 pacientes. Se recolectaron variables microbiológicas y sociodemográficas de pacientes diagnosticados con cáncer en las sedes de Pereira, Armenia, Manizales y Cartago de Oncólogos de Occidente S.A. durante 2.014 hasta 2.016. Los perfiles de resistencia bacteriana se definieron de acuerdo con la guía CLSI. Los focos de cultivo fueron sangre, orina, biopsias de tejidos, piel y tejidos blandos, membranas mucosas y heces.

Resultados: La tasa de cultivo positivo fue del 27,94%. De 2.190 aislamientos, E. coli (22,42%) fue el más frecuente, seguido de K. pneumoniae (21,27%), P. aeruginosa (13,83%) y S. aureus (5,11%). Los principales mecanismos de resistencia identificados en Gram negativos fueron β-lactamasas de espectro extendido (45,45%) y β-lactamasa de tipo AmpC (37,71%).

Discusión: Cerca de un tercio de los cultivos de los participantes fueron positivos y una vasta mayoría fueron gram negativos, provistos con ESBL o AmpC, lo que en pacientes oncológicos es un desenlace catastrófico. Recomendamos establecer políticas de dispensación de antibióticos, logrando así un control de riesgo microbiológico y mejorar la vigilancia epidemiológica. No se recomienda el uso empírico de betalactámicos con espectro extendido o cefalosporinas de 1 a 3 generación debido a la alta tasa de resistencia encontrada.

Palabras clave: Neoplasias; Infección hospitalaria; Farmacorresistencia microbiana; Instituciones oncológicas; Antibióticos.

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Introduction

The development of new therapies for oncological patients has generated an increase in life expectancy, but in the same way, this has led to a higher risk of infection. The high rates of infections are a result of several conditions like cancer chemotherapy, immunosuppressants, neutropenia, surgeries, malnutrition, chronic inflammatory diseases, organ transplantation and a greater exposure to invasive techniques such as catheters, dialysis and respiratory support, due to the increase in the length of their hospital stays[1,2].

Antibiotic resistance is one of the most important public health problems in the world. Its origin is multifactorial. The main associated aspects described are an inappropriate use, the lack of effective surveillance systems, the absence of legislation to regulate the market, and its widespread use in animals[3-5]. Nowadays, antimicrobial resistance tests are crucial to determine empirical and non-empirical therapy schemes that should be followed by health professionals. Worst case scenario, a pathogen develops resistance against three or more classes of antibiotics, making it multi-resistant, an increasing daunting situation, without many pharmacological alternatives available[3,4,6-10].

The pattern of infectious disease in cancer patients has changed over time. Back in the early 1.980s, Gram-negative microorganisms were responsible for nearly two-thirds of infections; however, at the end of that decade, the pattern changed, being overtaken by Gram-positive ones. In this case, there is a reappearance of multi-resistant Gram-negative bacteria[5,11]. Otherwise, Gram-positive infections mortality ranges from 5% to 20%[12-14], compared with 18 to 40% for Gram-negative ones[3,15].

In Colombia, 80.000 new cases of cancer were diagnosed in 2.015; a trend expected to increase by 2.035 in 155.000 new cases per year[16]. Furthermore, it is also expected an increase in infections prevalence, antibiotics use, antibiotic therapy resistance and associated mortality. As a disadvantage, the country has a small number of reference centers that publish epidemiological, clinical and microbiological behaviors about this population, and when compared, there are discrepancies with international reports[17-20].

In our region, cancer has been establishing as a serious and growing public health problem, occupying the first causes of morbidity and mortality in the Colombian population. *Oncologos de Occidente*, an institution that covers between 85% and 95% of patients with cancer of the Colombian coffee region area, facilitates the study of their cancer clinical records, in order to design screening interventions and reduce the rates of associated morbidity and mortality[21].

For this reason, a cross-sectional study was carried out analyzing the microbiological characteristics of infections in patients from an oncological reference center in the Colombian coffee region area during 2014-2016.

Patients and methods

A cross-sectional, descriptive study on microbiological isolates from cancer patients during a 3-year period in Colombia was realized. Our study group was established by patients over 18 years old with histopathologically cancer diagnosis (include hematological malignancies); treated in *"Oncólogos del Occidente S.A."* located in Armenia, Manizales, and Pereira (Colombia) from January 2014 to December 2016; who had suffered an infectious process defined as patients with fever, neutrophil count below 1.500/mm3[1] or any other cause of clinical suspicion of infection during their hospital stays; and that, were systematically cultivated with antibiogram to confirm an infectious focus.

Laboratory procedures

Samples were processed at the Oncólogos del Occidente S.A. Microbiology tests were performed using automatic BACTEC systems. If there was a high suspicion of colonization or bacterial contamination, the process was restarted from the sowing in the respective agars to the identification of the agent, with the subsequent clinical and paraclinical correlation that allowed verifying the infection. All the processes performed by the laboratory were standardized.

Source of information

The "*Sistema de Administración de Historias Clínicas Oncológicas" (*SAHICO) by its initials in Spanish, is the registration system used by Oncólogos del Occidente S.A. to store their medical records. The laboratory, based on the Performance Standards for Antimicrobial Susceptibility Testing (CLSI 2015 guideline)[22], reported through the software WHONET 5,6: date of the sample collection, source of the positive sample, etiological agent, minimum inhibitory concentration, antimicrobial in-vitro resistance development, and bacterial resistance.

Statistical analysis

With the identification of patients, the databases of SAHICO and WHONET were mixed. Medians and interquartile range (IQR) of continuous and discrete variables were examined. Nominal variables were analyzed using absolute and relative frequencies. All analyzes were performed using STATA 14,2 official version.

Ethics approval

Approved by the Bioethics Committee of the Universidad Tecnológica de Pereira[23] and the Infections Committee of Oncólogos del Occidente S.A. The authors declare that there is no conflict of interest.

Results

From January 1, 2014, to December 31, 2016, we collected data on over 1.216 patients with cancer diagnosis from a reference oncological institution in three cities from Colombia. The 51,97% (n=632) were females compared to 48,03% (n=584) males. The mean age was 58,79 ± 17,83 years (ran-

ge: 18-95 years) with the following distribution: <20 years (n=24, 1,97%); 20-44 years (n=228, 18,75%); 45-65 years (n=463, 38,08%); and ≥65 years (n=501, 41,20%). A total of 7.837 cultures made during the study period. The service with the largest number of cultures requested was hospitalization (66,88%; n=5.241), followed by the Intensive Care Unit (30,48%; n=2.389), operating rooms (2,07; n=162) and external consultation (0,57%; n=45). The culture positive rate was 27,94% (n=2.190) and 72,06% (n=5.647) were negative; of those, 6.938 samples (88,53%) were obtained before starting antibiotic therapy. The table 1 shows the culture positivity according to sample type.

Of all infections, 79,54% (n=1.742) were a Gram-negative bacterium, 15,71% (n=344) were a Gram-positive bacterium and 4,74% (n=104) had a yeast like fungi. Main one's isolated bacteria were described in Table 2.

According to sample type, we found that for *E. coli:* 41,14% (n=202) corresponded to a blood culture; 31,57% (n=155) to urine culture and 10,39% (n=51) to skin and mucous membranes samples. For *K. pneumoniae* we reported: 63,73% (n=297) corresponded to blood culture, 17,17% (n=80) to urine culture and 6,65% (n=31) to respiratory tract. For *P. aeruginosa:* 49,50% (n=150) to blood cultures, 23,43% (n=71) to urine culture and 9,90% (n=30) to respiratory tract samples. For *S. aureus:* 81,25% (n=91) to blood culture, while 11,60% (n=13) corresponded to biopsy and tissue samples.

We performed a blood culture analysis to identify the most prevalent pathogens, recognizing *Klebsiella pneumoniae* (22,93%, n=297), *Escherichia coli* (15,60%; n=202), *Pseudomonas aeruginosa* (11,58%; n=150) and *Staphylococcus aureus* (7,03%; n=91).

The Table 3 shows the most prevalent profiles of antibiotic resistance founded in Gram-negative bacteria. The main mechanisms of antibiotic resistance reported for Gram-negative are extended-spectrum β-lactamases (ESBLs) (45,45%; n=235) and AmpC-type 7β-lactamases (AmpC) (37,71%; n=195); Otherwise, for Gram-positive the 47,20% (n=116) were methicillin-resistant Staphylococcus aureus (MRSA).

Table 1. Culture positivity according to sample type

Samples	Positive cultures n (%)	Negative cultures n (%)	Total Cultures N (%)
Blood	1295 (22.93)	4353 (77.07)	5648 (72.07)
Urine	447 (33.09)	904 (66.91)	1351 (17.24)
Biopsy and tissues	120 (57.42)	89 (42.58)	209 (2.67)
Body liquids	82 (40.00)	123 (60.00)	205 (2.62)
Respiratory samples	62 (34.25)	119 (65.75)	181 (2.31)
Skin and mucosa	105 (76.64)	32 (23.36)	137 (1.75)
Stool	79 (74.53)	27 (25.47)	106 (1.35)
Total	2190 (27.94)	5647 (72.06)	**7837**

Table 2. Isolated bacteria with higher prevalence

Gram negatives	n (%)	Gram positives	n (%)
Escherichia coli	491 (22.42)	*Staphylococcus aureus*	112 (5.11)
Klebsiella pneumoniae	466 (21.28)	*Enterococcus faecalis*	60 (2.74)
Pseudomona aeruginosa	303 (13.84)	*Staphylococcus epidermidis*	49 (2.24)
Enterobacter cloacae	104 (4.75)	*Staphylococcus haemolyticus*	18 (0.82)
Proteus mirabilis	43 (1.96)	*Enterococcus faecium*	14 (0.64)

Discussion

To our knowledge, this is the first study on microbiological characterization of infections in oncological patients from a reference center in Colombia. We found that up to nearly one-third of our participants' cultures were positive and a vast majority were gram-negative agents, provided with ESBLs or AmpCs as mechanisms of antibiotic resistance. According to these results, we can assure that, if in the general population the antimicrobial resistance is a matter of public health, in oncological patients it is a catastrophic outcome.

There is a lack of research in Latin America about microbiological characteristics of infections in this group and by the time we checked there was only one conducted in Mexico with 45,4% ESBLs producers, 1,8% carbapenemase-resistant, and *E. coli* as most frequent microorganism isolated (42,3%)[24]. Our findings showed *E. coli* (22,42%) as the prevalent Gram-negative bacteria, 45,45% ESBLs and AmpC 37,71% producers in the same group, which resembles the previous mentioned study and others from countries with similar socio-demographic conditions in which predominated *E. coli (*22,2% Sudan, 28% Cuba)[4,24,25] and ESBLs production of 49,2%[4]; whereas a research conducted in Spain to assessed multi-resistant gram-negative bacteremia exposed production rates of 80% ESBLs and 8% AmpC[8]. Made an impression the low rate of isolation of carbapenemase-producing gram-negative bacilli and that there is no previous report of it in our region[26].

We also found that *S. aureus* was the gram-positive bacteria with greater isolation (5,11%), this fits previous studies with prevalences between 7,9%-20,2%[4,27]. We were able to determine 47,2% (n=116) MRSA which is different than previous reports in Mexico, wherein 90% were MRSA[6]. These results suggest that the implementation of prophylactic and therapeutic antibiotic regimens in oncological centers, hand in hand with early de-escalation of high-spectrum antibiotics, is preventing the expansion of MRSA, bearing in mind that a 47% rate is quite alarming.

Table 3. Resistance profile of most frequently isolated Gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae and Pseudomona aeruginosa). TPM/SMX: Trimethoprim Sulfamethoxazole

Gram negative bacteria	Percentage (%)		
	Sensitive	Medium	Resistant
Escherichia coli (n=491)			
Ampicillin	25.3	0.4	74.3
Amoxicillin-clavulanate	52.6	9.5	37.9
Piperacillin-Tazobactam	89.9	4.1	6.0
Cefazolin	60.7	6.0	33.3
Cefalotin	19.8	17.7	62.5
Cefuroxime	58.5	2.0	39.5
Ceftazidime	65.5	1.6	32.9
Ceftriaxone	63.5	0.0	36.5
Cefepime	71.2	0.8	28.0
Aztreonam	66.2	4.0	29.8
Meropenem	96.3	0.4	3.3
Gentamicin	84.2	5.3	10.5
Ciprofloxacin	60.8	0.4	38.8
Levofloxacin	61.3	0.2	38.5
TPM/SMX	52	0.0	48.0
Klebsiella pneumoniae (n=466)			
Ampicillin	1.5	0.6	97.9
Amoxicillin-clavulanate	58.0	9.0	33.0
Piperacillin-Tazobactam	71.4	6.8	21.8
Cefazolin	50.0	2,4	47.6
Cefalotin	47.0	3.9	49.1
Cefuroxime	62.7	2.8	34.5
Ceftazidime	70.8	1.1	28.1
Ceftriaxone	67.6	0.9	31.5
Cefepime	72.2	0.9	26.9
Aztreonam	73.3	0.3	26.4
Meropenem	95.7	0.9	3.4
Gentamicin	84.8	4.5	10.7
Tigecycline	94.1	5.2	0.7
Ciprofloxacin	79,8	5,5	14,7
TPM/SMX	75.1	0.0	24.9
Pseudomonas aeruginosa (n=303)			
Piperacillin-Tazobactam	66.8	11.9	21.3
Ceftazidime	64.3	5.6	30.1
Cefepime	66.1	5.9	28.0
Aztreonam	61.5	4.9	33.6
Meropenem	63.3	9.1	27.6
Ciprofloxacin	68.5	0.4	31.1

According to the evidence the high negative blood culture in our study can be explained by patient´s self-medication, prophylactic therapy or antibiotic therapy on admission, reflected with a culture positivity of 27,94%, which is similar to reported studies[28,29]; with an average of 1.8 positive cultures per patient, greater than 0,04 -1,64 documented[6,11,27,28]. Nevertheless our findings on bacterial isolation (Gram-negative 79,54%, Gram-positive in 15,71% and fungus in 4,74%), contrasted with other studies with distributions as Gram-positive (26,70% - 76,10%), Gram-negative (23,90% - 60,23%) and fungi (11,90% – 14%)[8,11,28-30]. These data supports the shift from gram-positive to gram-negative agents in our region, which may suggests an apparently adequate management of central venous accesses, a failure in biosafety and sanitation protocols, a lack of antibiotic prophylaxis with fluoroquinolones in neutropenic patients or even worse, a significantly increase in resistance for them, as seen in our findings with a ciprofloxacin resistance of 38,8% for *E. coli* and 14,7% for *K. pneumoniae*. This resistance pattern is commensurable with the reported in an investigation made in Taiwan (2010), where the Gram-negative prevalence was 60%[29].

We could not correlate the clinical information and the microbiological characteristics due to the absence of the former in our database, main limitation of our retrospective study, this is a possibility that remains to be execute in cohorts that allow rigorous long term follow up of patients to assess variables that we missed: type of cancer, venous access (central or peripheral line), hospital stay, pharmacotherapies, related costs and survival rates, between others.

The present study defined the pathogens' characteristics of infections in a population with oncological diagnosis which allow us to do the next conclusions. According to our findings, we recommend prior taking of cultures, the beginning of empirical treatment with coverage for Gram negative such as *Escherichia coli, Klebsiella pneumoniae* and *Pseudomona aeruginosa;* establishing antibiotic dispensing policies (plus therapeutic de-escalation) thus achieving a microbiological risk control and improve the epidemiological surveillance. Empirical use of beta-lactams with extended spectrum or cephalosporins of 1 to 3 generation is not recommended due to the high resistance found. Alternatively, if resistance to an antibiotic group already exists, we would suggest to start a cyclic replacement, which is performed with antibiotics of different mode of action until the resistance to the former relapses[5,7,10,26,30,31].

Ethical disclosures

Protection of human and animal subjects. No experiments were performed in animal nor humans.

Confidentiality of data. Patient´s data were anonymized

Competing interests. None declared.

Funding sources. None.

Ethical approval. This research was approved by the Ethics Committee of the University.

Conflict of interest. The authors have no conflicts of interest to declare.

References

1. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol.* 2008;29(11):996-1011.
2. Ramos JR, Artés JSF, Andrés JLP, Sánchez ER, Lletí MS, Castellanos-Ortega Á, et al. Impacto de un programa de optimización de antimicrobianos sobre el paciente crítico hematológico. *Farm Hosp.* 2017;41(4):479-487.
3. Ruhnke M, Arnold R, Gastmeier P. Infection control issues in patients with haematological malignancies in the era of multidrug-resistant bacteria. *Lancet Oncol.* 2014;15(13):e606-e619.
4. Nurain AM, Bilal NE, Ibrahim ME. The frequency and antimicrobial resistance patterns of nosocomial pathogens recovered from cancer patients and hospital environments. *Asian Pac J Trop Biomed.* 2015;5(12):1055-1059.
5. Gómez-Gonzalez JF, Sánchez-Duque JA. Perfil microbiológico y resistencia bacteriana en una unidad de cuidados intensivos de Pereira, Colombia, 2015. *MÉD UIS.* 2018;31(2):9-15.
6. Cornejo-Juárez P, Vilar-Compte D, Pérez-Jiménez C, Namendys-Silva S, Sandoval-Hernández S, Volkow-Fernández P. The impact of hospital-acquired infections with multidrug-resistant bacteria in an oncology intensive care unit. *Int J of Infect Dis.* 2015;31:31-34.
7. Cataño-Toro D, Martínez JW, Martínez-Muñoz MA, López-Osorio JJ, Marín-Medina DS, Orozco-Hernández JP, et al. Factores de riesgo para mortalidad en la infección por Pseudomonas aeruginosa en pacientes oncológicos hospitalizados en tres ciudades de Colombia. *Rev MedUNAB.* 2017:20(1):39-47.
8. Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Cisnal M, Sánchez-Ortega I, et al. Bacteremia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. *J Antimicrob Chemother.* 2011;66(3):657-663.
9. de Oliveira Costa P, Atta EH, da Silva ARA. Infection with multidrug-resistant gram-negative bacteria in a pediatric oncology intensive care unit: risk factors and outcomes. *J Pediatr.* 2015;91(5):435-441.
10. Rodriguez-Morales AJ, Martinez-Pulgarin DF, Muñoz-Urbano M, Gómez-Suta D, Sánchez-Duque JA, Machado-Alba JE. Bibliometric Assessment of the Global Scientific Production of Nitazoxanide. *Cureus.* 2017;9(5):e1204.
11. Åttman E, Aittoniemi J, Sinisalo M, Vuento R, Lyytikäinen O, Kärki T, et al. Etiology, clinical course and outcome of healthcare-associated bloodstream infections in patients with hematological malignancies: a retrospective study of 350 patients in a Finnish tertiary care hospital. *Leuk Lymphoma.* 2015;56(12):3370-3377.
12. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin infect dis.* 2011;52(4):e56-e93.
13. Lingaratnam S, Slavin M, Koczwara B, Seymour J, Szer J, Underhill C, et al. Introduction to the Australian consensus guidelines for the management of neutropenic fever in adult cancer patients, 2010/2011. *Intern med j.* 2011;41(1b):75-81.
14. Mandal PK, Maji SK, Dolai TK, De R, Dutta S, Saha S, et al. Micro-organisms Associated with Febrile Neutropenia in Patients with Haematological Malignancies in a Tertiary Care Hospital in Eastern India. *Indian J Hematol Blood Transfus.* 2015;31(1):46-50.
15. Freire M, Pierrotti L, Ibrahim K, Magri A, Bonazzi P, Hajar L, et al. Infection with Klebsiella pneumoniae carbapenemase (KPC)-producing Klebsiella pneumoniae in cancer patients. *Eur J Clin Microbiol Infect Dis.* 2015;34(2):277-286.
16. Wiesner C. La atención del cáncer desde la perspectiva de la sostenibilidad financiera del Sistema General de Seguridad Social en Colombia. *Rev colomb cancerol.* 2016;20(2):49-51.
17. Puentes GA, Quiroga C, Álvarez CA, Támara JR, Ruiz Á. Características demográficas, morbilidad y mortalidad de los pacientes adultos con neutropenia febril tratados con cefepima. *Rev chilena infectol.* 2012;29(3):322-328.
18. Maya M, Octavio G, Rodelo Vélez AM, Carvajal JJ, González JM, Jaimes Barragán FA. Características clínicas y microbiológicas de los pacientes neutropénicos febriles con neoplasias hematológicas. *Iatreia.* 2008;21:s9-s.
19. Cortés JA, Cuervo S, Gómez CA, Bermúdez D, Martínez T, Arroyo P. Neutropenia febril en el trópico: una descripción de los hallazgos clínicos y microbiológicos y el impacto de la terapia inapropiada que utilizan en un centro de referencia oncológica en Colombia. *Biomédica.* 2013;33(1):70-77.
20. Cortés JA, Cuervo SI, Arroyo P, Quevedo R. Hallazgos microbiológicos en pacientes con neutropenia febril. *Rev Colomb Cancerol.* 2003;7(4):5-11.
21. Martinez JW, Moreno GA, de Los Ríos PA. Tendencia en el reporte de casos de cáncer en Oncólogos del Occidente, Pereira, Colombia. *Rev Med Risaralda*. 2012;18(2).
22. Wayne P. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. CLSI Document M100-S25, Clinical and Laboratory Standards Institute. 2015.
23. Ministerio S. Artículo 11 de la resolución 008430 de 1993, por la cual se establecen las normas científicas, técnicas y administrativas para la investigación en salud. Bogotá. *Rev Colomb Psiquiatr.* 1993;1996;25:38-59.
24. Islas-Muñoz B, Volkow-Fernández P, Ibanes-Gutiérrez C, Villamar-Ramírez A, Vilar-Compte D & Cornejo-Juárez P. Bloodstream infections in cancer patients. Risk factors associated with mortality. *Int J Infect Dis.* 2018; 71, 59-64.
25. Almenares Elías B CQMC, Lavado Fernández J A, Padilla Arencibia M, Edward Seringe S. Infección intrahospitalaria en pacientes con cáncer. *MEDISAN.* 2010; (14) 2026-2030.
26. Polinski J, Harmon S, Henderson K, Barker T, Sussman A, Gagliano N. Antibiotic stewardship in the retail clinic setting: Implementation in 1100 clinics nationwide. *Healthcare* (Amsterdam, Netherlands). 2017;5(3):89.
27. Velázquez Brizuela I E AGJ, Ortíz G G, Camacho Cortés J L. Epidemiología de infecciones nosocomiales en el Instituto Jalisciense de Cancerología. *Rev Cub Salud Pública.* 2013;(39)19-31.
28. Zarco-Márquez S, Volkow-Fernández P, Velázquez-Acosta C, Echániz-Avilés G, Carnalla-Barajas M, Soto-Noguerón A, et al. Invasive and Complicated Pneumococcal Infection in Patients with Cancer. *Rev invest clin.* 2016;68(5):221.
29. Chen C-Y, TSAY W, Tang J-L, Tien H-F, Chen Y-C, Chang S-C, et al. Epidemiology of bloodstream infections in patients with haematological malignancies with and without neutropenia. *Epidemiol Infect.* 2010;138(7):1044-1051.
30. Cataño-Toro D, Marin-Medina DS, Rivera J, Martínez JW, Sánchez-Duque JA, Martínez-Muñoz M, et al. Neutropenia febril en pacientes con neoplasias hematológicas de un centro de referencia en Colombia. *Salud Uninorte.* 2019; 35(2): in press.
31. Machado-Alba JM, Sanchez-Duque JA, Gómez-González JF, Moreno-Gutierrez PA, Pantoja-Meneses SA, Thahir-Silva S, et al. Trends of Antibiotic Consumption in Intensive Care Units of Colombia, 2010-2016. *Value Health.* 2018;21:S96-S7.