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Prevalence of germs with multi antibiotic resistance in bacteremia associated with febrile neutropenia in hospitalized cancer patients. A single-center study

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Abstract

Introduction: Cancer in 2020 caused 1.4 million deaths, 47% in people under 65 years of age, and febrile neutropenia in cancer patients increases cases of serious infections, increasing morbidity and mortality when timely treatment has not been initiated. The objective of the present study was to describe a population with this pathology in a regional reference center.

Methodology: This cross-sectional study was carried out at the National Oncology Institute "Dr. Juan Tanca Marengo," Society for the Fight Against Cancer, Solca -Guayaquil, January 2020- June 2021, with a nonprobabilistic sample of patients with neoplasms, neutropenia, and positive cultures. Demographic, clinical, and laboratory variables were recorded. Descriptive statistics are used univariate.

Results: A total of 126 cases were analyzed, with an average age of 55 years; 50.8% were female; 88.1% were admitted with febrile neutropenia; and the average hospital stay was seven days. Escherichia coli was the most frequent microorganism (17.5%), followed by Klebsiella pneumoniae (9.5%), Enterobacter aerogenes, and Pseudomonas aeruginosa (4.8%). A total of 70.2% of the isolated bacteria presented bacterial resistance, 47% were extended-spectrum beta-lactamase bacteria (ESBL), 40% were extended-spectrum beta-lactamase (ESBL), 5% produced carbapenemases (KPC), and 57.5% with bacterial resistance had a hospital stay greater than seven days.

Conclusion: The main microorganism was Escherichia coli, and resistance was primarily found in extended-spectrum beta-lactamase-positive bacteria, allowing us to know the local epidemiology of the microbiological profile and its relationship with cancer patients with febrile neutropenia.

Keywords:
MeSH: Neutropenia, Febrile Neutropenia, Chemotherapy-Induced Febrile Neutropenia, Neoplasms; Blood Culture.

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Introduction

Cancer is one of the diseases that produces the highest mortality worldwide; in 2020, it will cause 1.4 million deaths, 47% in people under 65 years of age [1]. Cancer is caused by genetic alterations that result in dysregulation of cell growth and division [2]. Chemotherapy acts on cells that present accelerated cell division and growth, causing cytotoxicity, especially in the medullary cellular architecture, whose secondary effect will be myelosuppression, which will be directly proportional to the dose, drugs, route of administration, age, nutrition, medullary physiology, and history of chemotherapy [3].

The presence of neutropenia in the context of an oncological patient will increase the cases of serious infections, including sepsis and bacteremia, which aggravate the underlying pathology and increase morbidity and mortality, especially in cases where no treatment has been started. A timely manner endangers the life of the patient [4].

Febrile neutropenia (FN) is an oncological emergency related to a more extended hospital stay, even in intensive care areas, with the consequent increase in nosocomial infections, development of drug resistance, production, and increased medical costs [5].

Neutropenia symptoms are related to factors such as the type of tumor, the presence of comorbidities, the extent of the disease, and adverse reactions to the type of treatment. It is essential to categorize patients at low and high risk of suffering complications in the context of patients with febrile neutropenia, which would be very useful to generate therapeutic strategies and arrive at a coherent treatment depending on the magnitude of the disease, including the possibility of giving outpatient treatment in cases that meet clinical and analytical criteria that allow avoiding related opportunistic infections with hospitalization [6, 7].

In 2000, a prognostic scale called the MASCC (Multinational Association for Supportive Care in Cancer) was presented, which made it possible to identify patients with a low risk of complications in the context of patients with febrile neutropenia who had been endorsed by the IDSA (Infectious Diseases Society of America) and the ESMO (European Society for Medical Oncology) as a valuable tool for clinical practice in the management of patients with febrile neutropenia. However, some studies show limitations concerning some of its variables for being subjective and dependent on the observer [8]. The Clinical Index of Stable Febrile Neutropenia (CISNE) scale is another proposal to classify stable patients, and the use of scales will help us choose the best option for the treatment site [9].

Febrile neutropenia is a medical emergency that requires the administration of broad-spectrum antibiotics empirically during the first 60 minutes with subsequent monitoring, with the sole purpose of avoiding complications during the disease [10]. The most commonly isolated bacterial spectra in patients with febrile neutropenia changed from Gram-negative to Gram-positive bacteria; however, infections by Gram-negative bacteria with antibiotic resistance have increased [11].

In solid and hematological tumors in patients with NF, microbiological rescues play a fundamental role and constitute an invaluable tool for antimicrobial management; however,

the pattern of antimicrobial susceptibility directly affects the response to treatments administered practically [12]. Bacterial epidemiology and antibiotic resistance are essential when making clinical decisions, which is why local information based on a better therapeutic approach is needed.

This study aims to identify bacteria with multiantibiotic resistance in the antibiogram in patients with bacteremia concerning febrile neutropenia and its relationship with risk factors and mortality according to the microbiological profile treated in a single regional reference oncology center in the equator.

Materials and methods

Study design

Descriptive, analytical study; observational, cross-sectional.

Study area

The study was conducted in the clinical oncology department of the National Oncology Institute "Dr. Juan Tanca Marengo" from the Cancer Society, Solca-Guayaquil. The study period was from January 1, 2020, through June 30, 2021.

Universe and sample

The population was made up of patients admitted to the hospitalization of the institution. The sample calculation was nonprobabilistic for census-type convenience, in which all possible cases that can be analyzed are included.

Participants

Patients of legal age, solid or hematological tumors, and severe febrile neutropenia: the absolute value of neutrophils less than 500 cells/mm ^{3} were included with positive cultures from any of the following: blood, urine, feces, secretions. Records with incomplete data for analysis and patients with negative cultures were excluded.

Variables

Sociodemographic variables were included: age, sex, admission diagnosis, days of hospitalization, type of culture, type of bacteria cultured, bacterial resistance, and antibiogram.

Procedures, techniques, and instruments.

The data were collected from the clinical history in a form designed exclusively for that purpose. The institutional electronic system was used for case investigation. The database was coded with serial numbers, thus protecting the confidentiality of the information and identity of the patients. The cultures in the hospital above were analyzed with automated equipment within which the annual guidelines of the Clinical and Laboratory Standards Institute (CLSI) are taken into account to establish the cutoff point for bacterial resistance.

Bias avoidance

To guarantee the reliability of the information, the researchers were trained in data collection. A double checklist was used to include all cases. The data were validated and curated by the

researchers Carlos Soliz Poveda, Carlos Calle Caamaño, Ena Coloma Coloma, Andrea Plaza Rodríguez, and Norma Castro Ramírez. To avoid possible interviewer, information, and memory biases, the data were guarded at all times by the principal investigator with appropriate guidelines and records. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the hemodialysis sessions of the period above were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their agreement was verified.

Statistical analysis

Initially, a descriptive univariate analysis of the sample is performed. The statistical package was SPSS version 20.0 for PC (Armonk, NY: IBM Corp.) licensed to the researchers.

Results

Study participants

The study included 126 analyzable cases (Figure 1).

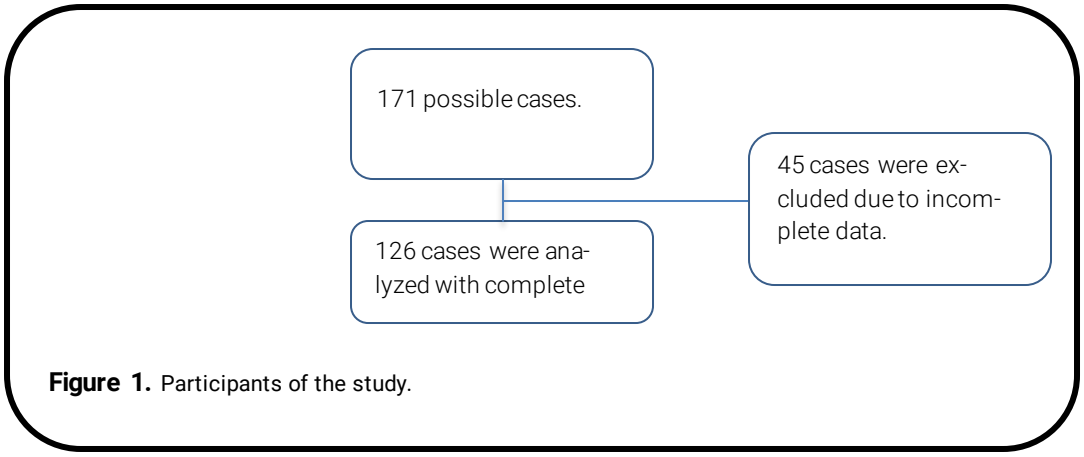

Figure 1. Participants of the study.

Sample characterization

The average age of the patients was 55 years, and more than 60% were older than 50 years; 50.8% were female, and 49.2% were male; 88.1% were admitted with febrile neutropenia; the average hospital stay was seven days, and more than 60% had more than six days of hospitalization (Table 1).

Table 1. Demographic and clinical characteristics of patients admitted with febrile neutropenia.

		N = 126	%
Age	Under 39 years old	25	19.8%
	From 40 to 49 years old	, twenty	15.9%
	From 50 to 59 years old	35	27.8%
	Older than 60 years	46	36.5%
Sex	Men	62	49.2%
	Woman	64	50.8%
Admission diagnosis	Afebrile Neutropenia	fifteen	11.9%
	Febrile neutropenia	111	88.1%
days of hospitalization	Less than five days	47	37.3%
	6 to 9 days	36	28.6%
	Greater than ten days	43	34.1%

Crops

Escherichia coli was the most frequent microorganism in the analyzed cultures, with 17.5%, Klebsiella pneumoniae with 9.5%, Enterobacter aerogenes and Pseudomonas aeruginosa with 4.8%, and Enterobacter cloacae with 1.6%; the other bacteria had percentages lower than 1% (Table 2). Of the total cultures analyzed, 52.4% had no bacterial growth, and the most frequent sites of infection were urine (15.9%), feces (12.7%), blood (7.9%), secretion (6.3%), skin and soft tissues (4%), and cerebrospinal fluid (0.8%).

Table 2. Isolated microorganisms with bacterial resistance in cancer patients with febrile neutropenia.

Bacterial resistance		
	%	N
Candida albicans	2.5%	1
Escherichia coli	22.5%	9
Enterobacter aerogenes	fifteen%	6
Enterobacter cloacae	5%	two
Enterococcus faecalis	2.5%	1
Staphylococcus aureus	0%	0
Staphylococcus epidermidis	2.5%	1
Klebsiella pneumoniae	22.5%	9
Moraxella lacunata	2.5%	1
Pseudomonas aureginosa	fifteen%	6
Serratia fonticola	2.5%	1
Staphylococcus aureus	2.5%	1
Staphylococcus intermedius	2.5%	1

Table 3. Antibiogram and bacterial resistance in cancer patients with febrile neutropenia.

	n=40	Percentage
ESBL +	19	47%
ESBL+	16	40%
KPC	two	5%
Cefoxitin +	3	8%

KPC: Klebsiella pneumoniae carbapenemase. ESBL: extended spectrum beta-lactamase. ESBL:' extended spectrum beta-lactamase

Type of bacteria according to the site of infection in cancer patients with febrile neutropenia. Escherichia coli was found in 41% of urine cultures, Klebsiella pneumoniae in 42% of urine cultures and 25% in blood; Enterobacter aeruginosa was found in 33% of stool cultures, and Pseudomonas aeruginosa was found in 50% of secretion cultures.

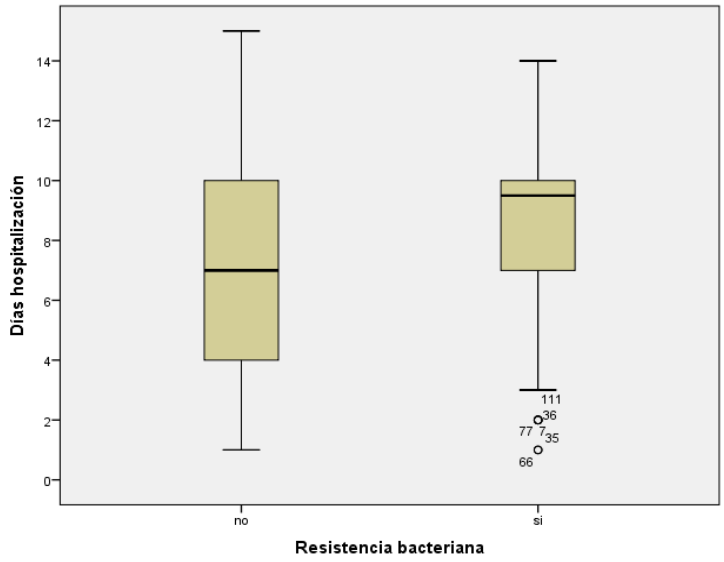

Figure 2. Box plot of the variable days of hospitalization according to bacterial resistance in cancer patients with febrile neutropenia in the study.

Isolated microorganisms with bacterial resistance in cancer patients with febrile neutropenia. Of the total bacteria isolated, 70.2% presented bacterial resistance. According to the type of bacteria with bacterial resistance, Klebsiella pneumoniae 75% and Escherichia coli 40.9% were resistant; the others, Enterobacter aerogenes, Enterobacter cloacae, Enterococcus, Staphylococcus epidermis, Moxarella lacunata, Pseudomonas aeruginosa, Serratia fonticola, Staphylococcus aureus, and Staphylococcus intermedius were 100% resistant.

Figure 2 shows the median days of hospitalization, with a longer hospitalization time in cultures with bacterial resistance, which has a median of 9 days; however, for cultures without bacterial resistance, the median is seven days.

Antibiogram and bacterial resistance in cancer patients with febrile neutropenia. Of the total bacteria isolated with resistance, 47% were extended-spectrum beta-lactamase (ESBL), 40% were extended-spectrum beta-lactamase (ESBL), and 5% produced carbapenemases (KPC) (Table 3).

Table 4. Risk factors associated with bacterial resistance in cancer patients with febrile neutropenia.

	%	N	p
days of hospitalization			
Less than seven days	42.5%	17	
Greater than or equal to 7 days	57.5%	23	
Prior chemotherapy treatment			
Yes	77.5%	31	
Nope	22.5%	9	
Previous antibiotic therapy			
Yes	47.5%	19	0.822
Nope	52.5%	twenty-one	

Risk factors associated with bacterial resistance in cancer patients with febrile neutropenia. Of the total number of bacteria with bacterial resistance, 57.5% of the patients had a hospital stay greater than seven days, 75% had a cancer diagnosis without comorbidities, 78% received prior chemotherapy treatment, 47.5% had a history of antibiotic therapy and 52.5% received prior antibiotic therapy. In turn, the chi-square statistical test was applied to identify the association of these risk factors with bacterial resistance, obtaining a *P value* of 0.001 for the variable days of hospitalization, which is less than the 0.005 level of significance; that is, the differences found between hospitalization time and bacterial resistance are statistically significant (Table 4).

Discussion

This investigation found that the most frequent microorganism was Escherichia coli in 17.5%, Klebsiella pneumonia in 9.5%, Enterobacter aerogenes, and Pseudomonas aeruginosa in 4.8%, at the same frequency. Of the total cultures analyzed, there was no bacterial growth in 52.4%, and the most frequent site of infection was urine in 15.9%, followed by feces in 12.7%. Of the total bacteria isolated, 70.2% presented bacterial resistance; according to the type of bacteria with bacterial resistance, it was Klebsiella pneumoniae 75% and Escherichia coli 40.9%.

This research, when compared with the prevalence of MDR germs in cancer patients in SOLCA Guayaquil, Cuenca, and Portoviejo hospitals carried out in 2020, in which they demonstrated the presence of Gram-positive, Gram-negative, or both germs; being the majority of the enterobacteria Escherichia coli, followed by Staphylococcus spp. Klebsiella spp. are heterogeneous since, currently, the prevalence of the MDR germ in this study was Klebsiella spp. [12, 13].

Similarly, this study is analogous to the investigation of febrile neutropenia in adult hemato-oncology patients in Colombia, whose purpose was to identify the clinical characteristics and microbiological findings in patients who are admitted or develop febrile neutropenia as a postchemotherapy complication; the results show that the age was 49 years old, and the frequently isolated germs were non-MDR Escherichia coli 25.5%, non-MDR Klebsiella pneumonia 10.7%, and coagulase-negative Staphylococcus 10.7% [11]. In the same way, in the characterization study of adult patients with febrile neutropenia carried out in a university hospital in Medellín, Colombia, between 2012 and 2016, it was determined that 96% had an underlying

oncological disease, with positive blood cultures of 31%, and the microorganism mainly isolated was Escherichia coli [12].

A divergence was found when relating the study carried out in the institution with the profile of bacterial resistance and mortality in oncohematological patients with postchemotherapy febrile neutropenia between 2016 and 2018 carried out at the Eugenio Espejo specialty hospital in Quito-Ecuador, which showed that of 157 patients, the prevalence was 58.6% for MDR germs, in which ESBL-producing Escherichia coli was the most frequently isolated microorganism, with 54.55%, as opposed to the most prevalent MDR germ in the institution, which was Klebsiella pneumonia, with 75% [14, 15]. Likewise, it is similar to the characterization study of infections in adult cancer patients treated with chemotherapy at the "José Carrasco Arteaga" Hospital in Cuenca, Ecuador; it is shown that it presented a higher prevalence of MDR germs in women aged between 61 and 80 years. In this case, the most frequent infections were of the bacterial type. The microorganisms mainly involved are Gram-negative bacilli such as Escherichia coli and Gram-positive cocci such as Staphylococcus aureus; the site of infection is usually the urinary tract [16].

Contrary to what was evidenced in Paraguay, the causal agents of bacteremia in adult patients with febrile neutropenia at the Hospital de Clínicas in Paraguay had an average age of 38 years, with 40% bacteremia, with a predominance of great positive cocci; the most frequently isolated microorganisms were Klebsiella pneumonia and Staphylococcus aureus [1 3]. Unlike the characterization of oncological patients with febrile neutropenia at the FISA High-Tech Oncology Center in Barranquilla, Colombia, it had a higher prevalence in women (60%), the mean age was 48 years, and lymphoblastic leukemia was the most frequent. most frequently with 45% [14].

It should be noted that this study was carried out promptly for bacteremia, and it would be essential to extend it to other microorganisms to obtain a comprehensive view of this type of patient.

It is suggested that, according to the evidence of these results, adequate policies can be developed to manage antibiotics in cancer patients with febrile neutropenia. Epidemiological investigations of bacterial resistance should be continued to develop clinical and therapeutic guidelines for cancer patients with febrile neutropenia to reduce morbidity and mortality in this type of patient.

Conclusions

In conclusion, the clinical characteristics of the cancer population were similar to those of the international literature, with some differences being found in terms of isolated microorganisms and microbial resistance; the main microorganism was Escherichia coli, and resistance was mainly beta-lactamase positive, allowing us to know the local epidemiology of the microbiological profile, in addition to identifying the prevalence of MDR bacteria and their relationship with cancer patients with febrile neutropenia.

Abbreviations

KPC: Klebsiella pneumoniae carbapenemase.
ESBL: extended spectrum beta-lactamase.
ESBL: extended spectrum beta-lactamase.
FN: febrile neutropenia

Administrative information

Additional Files

The authors declare none.

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Author contributions

1. Conceptualization: Carlos Calle Caamaño.
2. Formal analysis: Ena Coloma Coloma.
3. Research: Carlos Soliz Poveda.
4. Methodology: Carlos Calle Caamaño.
5. Project administration: Carlos Calle Caamaño.
6. Supervision: Norma Castro Ramirez.
7. Validation: Ena Coloma Coloma.
8. Visualization: Andrea Plaza Rodríguez.
9. Writing - draft or original: Andrea Plaza Rodríguez.
10. Writing - revision and editing: Ena Coloma Coloma – Andrea Plaza Rodríguez.

All authors read and approved the final version of the manuscript.

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Availability of data and materials

Data availability is available upon request to the corresponding author. No other materials were reported.

Statements

Ethics committee approval

It does not apply to observational studies with databases or medical records reviews.

Consent to publication

This does not apply to studies that do not publish explicit images such as CT scans, MRIs, and physical exam images.

Conflicts of interest

The authors declare that they have no conflict of interest or competence.

References

1. DeSantis CE, Miller KD, Dale W, Mohile SG, Cohen HJ, Leach CR, Goding Sauer A, Jemal A, Siegel RL. Cancer statistics for adults aged 85 years and older, 2019. CA Cancer J Clin. 2019 Nov;69(6):452-467. DOI: 10.3322/caac.21577. Epub 2019 August 7. PMID: 31390062.

2. Peralta-Zaragoza O, Bahena-Román M, Díaz-Benítez CE, Madrid-Marina V. Regulation of the cell cycle and the development of cancer: therapeutic prospects. Public Health Mex. 1997 Sep-Oct;39(5):451-62. Spanish. PMID: 9424727 .

3. Fontanella C, Bolzonello S, Lederer B, Aprile G. Management of breast cancer patients with chemotherapy-induced neutropenia or febrile neutropenia. Breast Care (Basel). 2014 Apr;9(4):239-45. DOI: 10.1159/000366466. PMID: 25404882 ; PMCID: PMC4209284.

4. Zimmer AJ, Freifeld AG. Optimal Management of Neutropenic Fever in Patients With Cancer. J Oncol Pract. 2019Jan;15(1):19-24. DOI: 10.1200/JOP.18.00269. PMID: 30629902.

5. Madrid C, Díaz L, Combariza J, Gálvez K, Olaya V, Ramírez I, Donado J. Epidemiology of febrile neutropenia in adult patients with hematological neoplasia, in a period of 26 months at Pablo Tobón Uribe Hospital, Colombia. Rev. chil. infectol. 2013;30(2):195-201. Scielo: 200010 . DOI: 10.4067/S0716 .

6. Manterola A., Romero P., Martínez E., Villafranca E., Arias F., Domínguez MA et al. Neutropenia and fever in the cancer patient. Anales Sis San Navarra 2004;27(Suppl 3):33-43. Scielo: S1137

7. Freifeld AG, Baden LR, Brown AE, Elting LS, Gelfand M, Greene JN, Ito JI, King E, Marcucci G, Montoya JG, Morris A, Noskin G, Rolston K, Schott AF, Segal B; National Comprehensive Cancer Network. Fever and neutropenia clinical practice guidelines. J Natl Compr Canc Netw. 2004Sep;2(5):390-432. DOI: 10.6004/jnccn.2004.0033. PMID: 19780251.

8. Carmona Bayonas A, Herrero Martínez JA, Martínez García J, Marín Vera M, Heras González M, De las, Navarrete Montoya A. Febrile neutropenia: analysis of prognostic factors and risk-adapted treatment. critical review. Oncology (Barc.) 2006;29(5):34-46. Scielo: S0378 .

9. Carmona-Bayonas A, Jiménez-Fonseca P, Virizuela Echaburu J, Antonio M, Font C, Biosca M, Et al. Prediction of serious patient complications with apparently stable febrile neutropenia: validation of the Clinical Index of Stable Febrile Neutropenia in a prospective cohort of patients from the FINITE study. J Clin Oncol. 2015 Feb 10;33(5):465-71. DOI: 10.1200/JCO.2014.57.2347. Epub 2015 January 5. PMID: 25559804.

10. Rivera-Salgado D, Valverde-Muñoz K, Ávila-Agüero M. Febrile neutropenia in children with cancer: management in the emergency service. Rev. chil. infectol. 2018;35(1):62-71. Scielo: S0716 . DOI: 10.4067/s0716 .

11. Braga CC, Taplitz RA, Flowers CR. Clinical Implications of Febrile Neutropenia Guidelines in the Cancer Patient Population. J Oncol Pract. 2019 Jan;15(1):25-26. DOI: 10.1200/JOP.18.00718. PMID: 30629901 ; PMCID: PMC6333383.

12. Osmani AH, Jabbar AA, Gangwani MK, Hassan B. Outcomes of High-Risk Patients with Febrile Neutropenia at a Tertiary Care Center. Asian Pac J Cancer Prev. 2017 Oct 26;18(10):2741-2745. DOI: 10.22034/APJCP.2017.18.10.2741. PMID: 29072402 ; PMCID: PMC5747398.

13. Cevallos J, Vera A. Comparative study on the prevalence of bacteremia affecting cancer patients in institutions in Solca Guayaquil, Portoviejo and Cuenca. Guayaquil. [Thesis – Pharmaceutical Chemist]. Institutional Repository of the University of Guayaquil. DSpace: 50938

14. Kala J, Finkel KW. Onconephrology. Crit Care Clin. 2021 Apr;37(2):365-384. DOI: 10.1016/j.ccc.2020.11.004. Epub 2021 February 13. PMID: 33752861.

15. Kumar BV, Mohan T. Retrospective Comparison of Estimated GFR using 2006 MDRD, 2009 CKD-EPI and Cockcroft-Gault with 24 Hour Urine Creatinine Clearance. J Clin Diagn Res. 2017 May;11(5): BC09-BC12. DOI: 10.7860/JCDR/2017/25124.9889. Epub 2017 May 1. PMID: 28658750 ; PMCID: PMC5483652.

16. McMahon BA, Rosner MH. GFR Measurement and Chemotherapy Dosing in Patients with Kidney Disease and Cancer. Kidney360. 2020 January 13;1(2):141-150. DOI: 10.34067/KID.0000952019. PMID: 35372903; PMCID: PMC8809099.