ORIGINAL ARTICLE

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EVALUATION OF ADHERENCE, SAFETY AND EFFECTIVENESS OF AN ANTIBIOTIC DE-ESCALATION STRATEGY IN PATIENTS WITH FEBRILE NEUTROPENIA DURING AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

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ABSTRACT

Introduction: There are ongoing concerns about optimal antibiotic regimens for febrile neutropenia during autologous hematopoietic stem cell transplantation (ASCT). **Objectives:** We assessed adherence, safety, and clinical outcomes of an antibiotic de-escalation protocol at a hematopoietic stem cell transplant reference center. **Methods:** We conducted a retrospective analysis of clinical data from 100 patients who developed febrile neutropenia during autologous stem cell transplantation between January 2020 and June 2021. In addition to presenting descriptive variables, we compared clinical outcomes, including treatment duration, hospitalization length, ICU admission, and mortality, among intervention groups. **Results:** Approximately 61% of the patients underwent the antibiotic de-escalation strategy, with an adherence rate of approximately 80% and only 20 protocol deviations. Comparing intervention groups, statistically significant differences favored the de-escalation and early termination group, which had shorter hospital stays (16 vs. 18 days, p 0.01) and fewer days of antibiotic treatment (5 vs. 8 days, p 0.006). There were no differences in safety outcomes. **Conclusions:** The antibiotic de-escalation strategy demonstrated significant adherence and proved to be safe and effective, with the added benefit of shorter hospital stays and reduced antibiotic exposure.

Keywords: Febrile neutropenia. Stem Cell Transplantation. Anti-Bacterial Agents. Drug Resistance, Microbial. Antimicrobial Stewardship.

INTRODUCTION

Autologous hematopoietic stem cell transplantation (auto-HSCT) is an accepted therapeutic option for the treatment of hematologic malignancies and some difficult-to-manage autoimmune diseases. This approach increases disease-free periods and/or improves overall survival by using high-dose chemotherapy, which leads to profound cytopenias with associated complications. Febrile neutropenia (FN) is not only very common but also remains a leading cause of early mortality associated with this treatment[1]. The accepted practice in these cases is the empirical use of broad-spectrum antibiotics until neutropenia resolves[2,3]. However, in this era of high bacterial resistance, there is significant interest in defining antibiotic use strategies that select the appropriate spectrum and duration, balancing the risk between inadequate coverage and resistance[4].

The main objective of this study is to describe the adherence, safety, clinical outcomes, and microbiological outcomes of implementing an antibiotic de-escalation protocol inspired by the guidelines of the Fourth European Conference on Infections in Leukemia (ECIL4)[5], in a group of patients undergoing auto-HSCT at a reference center in Colombia. As a secondary objective, and given that this is a study with retrospective real-life data, the different scenarios of protocol application were subcategorized and presented, and their relationship with different outcomes was analyzed to provide more resources for result analysis.

METHODS

A retrospective cohort study at Clínica Las Américas/AUNA in Medellín, Colombia, examined patients over 15 years of age, who underwent autologous transplantation between January 2020 and June 2021. The study focused on those who experienced febrile neutropenia during transplant hospitalization. Patients with incomplete data or pre-existing infections before transplant chemotherapy were excluded. The study was approved by the institutional ethics committee and endorsed by the clinical hematology program committee at the University of Antioquia. Informed consent was obtained from all patients.

Autologous transplant patients received care in isolated single rooms with contact precautions by medical and nursing staff. Vital signs and clinical evaluations occurred a minimum of 4 times daily for asymptomatic patients and more frequently when symptoms or complications were reported. Peripheral blood was the cell source, collected via a central venous catheter (subclavian or jugular) placed before conditioning. All patients received filgrastim support from the fifth day post-transplant until achieving three consecutive days with more than 500 neu/µL

Institutional protocol defined febrile neutropenia (NF) as having an absolute neutrophil count (ANC) ≤ 500 cells/µL and an isolated temperature ≥ 38.3ºC. Fever with a neutrophil count expected to reach the neutropenia threshold within 48 hours was also classified as NF (dynamic definition)[6].

Due to the high morbidity and mortality risk from extended-spectrum beta-lactamase (ESBL) germs in neutropenic patients[7-9], the protocol followed the ECIL-4 de-escalation recommendations, initiating meropenem (1 g IV every 8 hours) for NF, preceded by four blood cultures (2 aerobic, 2 anaerobic). De-escalation occurred if criteria were met within 96 hours, switching to narrower-spectrum antibiotics (Figure 1). If Gram-positive cocci were preliminarily reported in cultures, septic shock occurred, or there was a high risk of oxacillin-resistant cocci, it would lead to dual treatment with meropenem and vancomycin (or daptomycin).

"Early discontinuation" of antibiotics is defined as stoping the initial treatment within 96 hours without switching to other antibiotics. Failure to achieve defervescence within 96 hours of initiating first-line treatment is deemed as "*primary therapeutic failure*", prompting consideration for further interventions like escalating antimicrobial coverage.

"De-escalation failure" is confirmed if the fever reappears after de-escalation and the broader spectrum regimen is restarted. Methylprednisolone may be added if fever is suspected to be non-infectious[10].

FIGURE 1. De-escalation criteria and proposed de-escalation options in the institutional protocol

De-escalation criteria according to protocol:	1. Resolution of fever (defervescence) within the first 96 hours of initiating first-line treatment. 2. Absence of signs, symptoms, or paraclinical findings suggestive of sepsis or septic shock after initiation of first-line treatment. 3. Absence of signs, symptoms, or paraclinical findings suggestive of sepsis or septic shock after initiation of first-line treatment. Negative blood culture results or isolation of a germ sensitive to the antibiotic proposed for de-escalation within the first 96 hours of treatment.
First-line options	-Meropenem -Meropenem + vancomycin*
De-escalation options:	-Cefepime -Cefepime + vancomycin* -Vancomycin* as monotherapy -Discontinue all the antibiotics

*In some patients, daptomycin may be used as a replacement for vancomycin.

Treating physicians could request additional microbiological studies based on clinical context, like stool panels, urine analysis, culture, molecular tests, or imaging, to determine NF with or without an apparent focus[11].

Qualitative variables were described using absolute and relative frequencies, and comparisons were made using the $\chi 2$ test. The non-parametric Kruskal-Wallis test was used when comparing three or more groups. Quantitative variables were described with median and interquartile range values. The Mann-Whitney U test was employed after confirming non-parametric distribution through the Kolmogorov-Smirnov test. The significance level for statistical hypothesis testing was set at alpha 0.05. All analyses were performed using R software version 4.0.3 and RStudio 1.1.463

For clarity in the analysis of patients undergoing or not undergoing de-escalation, classification into intervention subgroups based on protocol adherence was proposed:

Definition of intervention groups according to protocol adherence:

Effective de-escalation (ED): Patients with febrile neutropenia who meet criteria and are successfully de-escalated by the treating physician to another antibiotic of lower spectrum.

Early suspension (ES): Patients with febrile neutropenia who meet de-escalation criteria and have antibiotics definitively discontinued within the first 96 hours of initiation as a de-escalation option.

Denial of de-escalation (DD): Patients with febrile neutropenia meeting de-escalation criteria but not de-escalated per treating physician's discretion.

De-escalation not contemplated (DNC): Patients with febrile neutropenia not meeting de-escalation criteria but de-escalated to another antibiotic against protocol.

Effective denial of de-escalation (EDD): Patients with febrile neutropenia not meeting de-escalation criteria and not de-escalated to another antibiotic effectively.

RESULTS

Participants

The institutional database included 109 adult patients who underwent autologous transplantation within the study period. Nine patients were excluded from the analysis: 2 due to insufficient data and 7 for not meeting the criteria for febrile neutropenia as an event of interest. Consequently, our analysis was based on the data of 100 patients.

Table 1 presents a comprehensive overview of patient characteristics, categorizing them based on the application of the de-escalation strategy. No statistically significant differences between the intervention subgroups were observed in clinical, sociodemographic, or primary diagnosis characteristics.

TABLE 1. Patient characteristics according to the application of the antibiotic de-escalation strategy

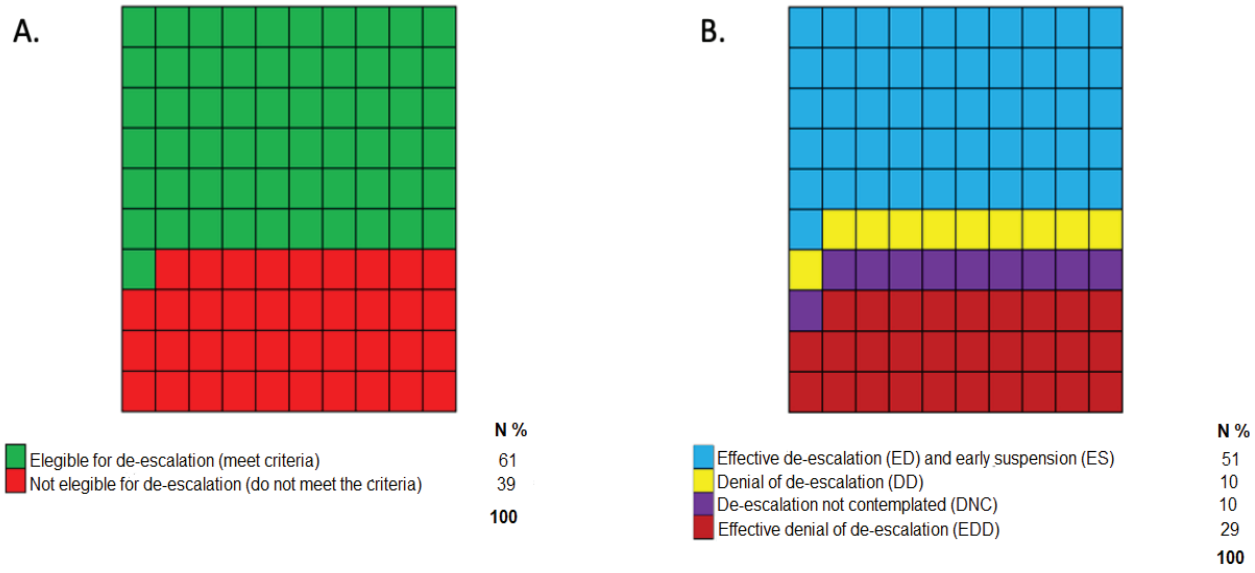
	De-escalation		
	Yes (n=61)	No (n=39)	
	n %	n %	P value
Age median (range)	56.6 (17-70)	55.9 (31-73)	0.64
Age group			
Adolescent (15-18)	1	0	0.52
Young adult (18-35)	5	2	
Middle Adult (35-65)	39	30	
Elderly (>65)	16	7	
Sex			
Female	34	25	0.53
Male	27	14	
Diagnosis			
Multiple Myeloma	40	23	0.30
Hodgkin's Lymphoma	6	2	
Non Hodgkin's Lymphomas	11	12	
Autoimmune Diseases	4	1	
Others	0	1	
ECOG			
0	1	0	0.14
1	45	26	
2	11	12	
Not defined	4	1	
DRI-TPH (SCT risk)			

Low	6	5	0.74
Intermediate	45	30	
High	1	0	
Undefined	9	4	
Disease Status			
Partial Response	31	14	0.16
Complete Response	26	24	
Non-Oncologic Disease	4	1	
Body Mass Index (BMI)			
Underweight	4	4	0.88
Normal Weight	28	16	
Overweight	20	14	
Obesity	9	5	
Antibiotic Prophylaxis			
Yes	14	9	1.0
No	47	30	

The absolute numbers are equivalent to the relative values because 100 patients were represented.

In total, 61% (61/100) of patients with NF underwent de-escalation, of which 83% (51/61) did so following the criteria established in the protocol (adherence proportion). This adherence proportion is depicted in green squares in Figure 2, which visually represents patient distribution based on eligibility criteria by protocol (A panel) and definitive intervention (B panel). The 80% (37/46) of de-escalations and 53% (8/15) of antibiotic treatment suspensions occurred before neutropenia resolution.

FIGURE 2. Distribution of patients according to de-escalation implementation. Panel A displays de-escalated patients in green and non-de-escalated patients in red. Panel B presents the specific distribution of patients according to protocol recommendations.



Clinical outcomes

Among the intervention groups based on antibiotic de-escalation, no statistically significant differences were found in the occurrence of sepsis (organ failure), admission to the intensive care unit, hospital readmission, or mortality at 30 or 100 days. However, it was found that the total days of hospital stay were shorter (16 vs. 18), and the total days of antibiotic use were reduced (5 vs. 8) among de-escalated patients compared to non-de-escalated ones, respectively.

There was 80% protocol adherence, and only 20 patients (20%) presented protocol deviations. In 10 patients, de-escalation was denied despite meeting the protocol criteria, while in the remaining cases, de-escalation occurred without indication.

Among sixty-one de-escalated patients, 20% (12/61) experienced at least one episode of fever after the antibiotic reduction. Interestingly, none of these fever recurrences happened in the patients de-escalated before neutrophil recovery. It is also important to note that 50% of these recurrences were observed in patients who underwent non-protocol de-escalation (6/10, 60%), while the remaining occurred in patients who were de-escalated as per protocol (6/51, 11%) (proportion difference p<0.0023). Only one case (1/12) of fever recurrence resulted in clinical de-escalation failure, necessitating reinstating the initial antibiotic spectrum; the rest were managed as immunologic fever (myeloid syndrome) without apparent adverse outcomes.

TABLE 2. Comparison of outcomes between intervention groups

Subgroup	General intervention groups		
	De-escalated (n=61)	Non-de-escalated (n=39)	p
Days of hospitalization	16 (12-54)	18 (13-28)	0.01
Antibiotic Duration	5 (2-11)	8 (5-14)	0.006
Documented infection	22	19	0.29
Organ failure	1	1	1
ICU/SICU	1	1	1
Hospital readmission (day of readmission)	2 (27 y 60)	3 (6, 25 y 76)	0.6
Infection with a germ resistant upon readmission	0	0	NA

Death during hospitalization	0	0	NA
30-day mortality	0	0	NA
100-day mortality	1	0	1
Composite outcomes (organ failure, readmission, and 100-day mortality)	4	4	0.774

ES ICU/SICU (Intensive Care Unit/Special Intensive Care Unit) (Intensive Care Unit)

Discussion

This study suggests that implementing an early termination and de-escalation of antibiotics protocol for auto-HSCT patients was feasible, safe, and effective in the real life seting. There were no statistically significant differences in adverse outcomes, including de-escalation failure, hospital readmission, ICU care, organ failure, recurrence of infection from resistant pathogens, or mortality during the first 100 days post-transplant between patients who underwent de-escalation and those who did not. Nevertheless, the de-escalation group did experience a shorter hospital stay and fewer days of antimicrobial exposure, which could be of significant benefit for transplantation units in terms of cost reduction and lower antibiotic exposure/resistance.

A randomized clinical trial by Aguilar-Guisado and colleagues in several Spanish transplant centers[12], including many autologous transplant patients, yielded similar results. They found that individuals who received the intervention of de-escalation or early termination of antibiotics did not experience more fever recurrences or higher mortality than controls. The experimental arm showed superiority with more antibiotic-free days (16.1 vs. 13.6 days, p 0.026) and a lower prevalence of adverse events.

The Nebraska group conducted a retrospective comparative study before and after implementing the ECIL-4 guideline recommendations[13]. While they reported no differences in mortality or hospitalization duration, there were differences in exposure to broad-spectrum antibiotics (3.09 vs. 4.69 days, p 0.069), favoring the early termination group. This group also had a lower reinfection incidence in the first 30 days post-transplant. It is important to note that this study did not clarify the distribution by transplant subtypes, and patients received prophylaxis with quinolones after the suspension of treatment, which differs from the protocol used in this study that did not involve prophylaxis after de-escalation without showing worse outcomes.

In 2019, Petteys et al. presented a retrospective study comparing early de-escalation and delayed suspension of antibiotics until neutrophil recovery[14], involving mostly autologous transplant patients. In both arms analyzed, there were no significant differences in recurrent fever (4.2% vs. 7.2%, p 0.85), bacteremia, rescaling (4.2 vs. 4.8%, p 0.64), in-hospital mortality (0 cases), or ICU admission (0 cases). However, unlike the present study, there was no reduction in treatment duration or hospitalization, possibly due to the uneven distribution of allogeneic transplant patients in the intervention arm, who typically have more extended periods of neutropenia and longer stays due to conditioning; this highlights the need to analyze transplant subtypes independently to avoid altering the results. We expect to present the results

of a parallel retrospective cohort of alo/haplotransplantation patients treated with the same febrile neutropenia protocol.

In France, Le Clech and collaborators presented the "How Long Study," which included 38 autologous transplant patients (31%)[15]. The study applied ECIL-4 recommendations in one group, requiring defervescence to suspend antibiotics. In contrast, antibiotics could be suspended five days after starting treatment in the other group, even if the patient still had a fever without a defined infectious focus. The primary composite outcome, including in-hospital mortality, ICU admission, infection with a resistant germ, or fever recurrence, did not differ between the two intervention groups (HR: 0.19-1.23, p = 0.11). In the current study, ten de-escalations were also out of protocol when the patient still had a fever, with no observed differences in adverse outcomes for this subgroup.

The adherence rate to the protocol of 80% in our study is considered satisfactory because it was not mandatory for the decision-making of the participant clinicians, and there were no on-time (or real time) feedback mechanisms during implementation. Similar studies in oncology achieved only partial adherence, ranging from 50% to 70%[16,17].

Another important aspect is that the proposed criteria for de-escalation were sensible, as patients classified as not suitable for de-escalation according to the protocol had a higher proportion of fever recurrences and microbiological isolations. This subgroup of patients represents a more uncomfortable scenario for clinicians, who usually prefer to be more prudent with antibiotic management in those cases. However, even this subgroup of patients did not present poor outcomes, raising questions about whether persistent or recurrent fever alone justifies deferring or limiting de-escalation strategies when the whole clinical condition and microbiological studies permit the contrary.

Notably, early suspension of antibiotics, considered a form of de-escalation, provided the most substantial benefits in reducing hospital stays and antibiotic use in the cohort. In this group, there were no instances of fever recurrence, even in cases where antibiotics were suspended before grafting.

The study had essential weaknesses, including being a single-center, retrospective study with a limited observation period, potentially introducing information biases and reducing external validity. The lack of microbiological analyses of colonization by resistant germs made it challenging to define the impact of interventions on patients' microbiota. Furthermore, using microbiological studies of readmissions as a proxy may underestimate this aspect. The study also faced challenges in establishing clinical and laboratory criteria for the early definition of fever origin or cause, as there are differential diagnoses for the febrile syndrome in patients undergoing auto-HSCT as myeloid reconstitution syndrome, adding complexity to the analysis. So, it is advisable to be cautious when applying these results more broadly.

In conclusion, the antibiotic protocol of early termination and de-escalation strategy in autologous transplant patients conducted at a Latin American HSCT unit demonstrated feasibility and significant adherence. This approach appeared to be safe and effective, reducing hospitalization days and exposure to broad-spectrum antibiotics. These findings align with data reported in international studies available in the literature.

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REFERENCES

1. Azoulay E, Mokart D, Pène F, et al. Outcomes of Critically Ill Patients With Hematologic Malignancies: Prospective Multicenter Data From France and Belgium—A Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique Study. J Clin Oncol. 2013;31(22):2810–8.

2. Freifeld AG, Bow EJ, Sepkowitz KA, 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):e56–93.

3. Zimmer AJ, Freifeld AG. Optimal Management of Neutropenic Fever in Patients With Cancer. J Oncol Pract. 2019;15(1):19–24.

4. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. Clin Infect Dis. 2017;65(11):1819–28.

5. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013;98(12):1826–35.

6. Bow EJ. Neutropenic Fever Syndromes in Patients Undergoing Cytotoxic Therapy for Acute Leukemia and Myelodysplastic Syndromes. Semin Hematol. 2009;46(3):259–68.

7. Kharrat M, Chebbi Y, Ben Tanfous F, et al. Extended spectrum beta-lactamase-producing Enterobacteriaceae infections in hematopoietic stem cell transplant recipients: Epidemiology and molecular characterization. Int J Antimicrob Agents. 2018;52(6):886–92.

8. Trecarichi EM, Tumbarello M, Spanu T, et al. Incidence and clinical impact of extended-spectrum-β-lactamase (ESBL) production and fluoroquinolone resistance in bloodstream infections caused by Escherichia coli in patients with hematological malignancies. J Infect. 2009;58(4):299–307.

9. Scheich S, Reinheimer C, Brandt C, et al. Clinical Impact of Colonization with Multidrug-Resistant Organisms on Outcome after Autologous Stem Cell Transplantation: A Retrospective Single-Center Study. Biol Blood Marrow Transplant. 2017;23(9):1455–62.

10. Miceli MH, Maertens J, Buvé K, et al. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: Proof of principle, description, and clinical and research implications. Cancer. 2007;110(1):112–20.

11. Satyanarayana G. Work-up for Fever During Neutropenia for Both the Stem Cell Transplant Recipient and the Hematologic Malignancy Patient. Infect Dis Clin North Am. 2019;33(2):381–97.

12. Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Lancet Haematol. 2017;4(12):e573–83.

13. Rearigh L, Stohs EJ, Freifeld A, et al. 2666. De-escalation of Broad-Spectrum Antibiotics in Hematopoietic Stem Cell Transplant Patients During Initial Episode of Febrile Neutropenia. Open Forum Infect Dis. 2019;6(Supplement_2):S934.

14. Petteys MM, Kachur E, Pillinger KE, et al. Antimicrobial deescalation in adult hematopoietic cell transplantation recipients with febrile neutropenia of unknown origin. J Oncol Pharm Pract. 2020;26(3):632–40.

15. Le Clech L, Talarmin JP, Couturier MA, et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. Infect Dis (Auckl). 2018;50(7):539–49.

16. Zuckermann J, Moreira LB, Stoll P, Moreira LM, Kuchenbecker RS, Polanczyk CA. Compliance with a critical pathway for the management of febrile neutropenia and impact on clinical outcomes. Ann Hematol. 2008;87(2):139–45.

17. Rosa RG, Goldani LZ, Santos RP. Association between adherence to an antimicrobial stewardship program and mortality among hospitalised cancer patients with febrile neutropaenia: a prospective cohort study. BMC Infect Dis. 2014;14(1):286.

APPENDIX 1

Subgroup	Specific intervention groups					
	ES (n=15)	ED (n=36)	DD (n= 10)	DNC (n=10)	ID (29)	p
Days of hospitalization	15	16	17	18	18	0.02
Antibiotic Duration	4	6	6	9	9	0.002
Documented infection	1	15	3	6	16	0.019
Organ failure	0	0	1	1	0	0.08
ICU/SICU	0	0	1	1	0	0.08
Hospital readmission (day of readmission)	0	2	0	0	3	0.46
Death during hospitalization	0	0	0	0	0	NA
30-day mortality	0	0	0	0	0	NA
100-day mortality	0	1	0	0	0	0.77
Composite outcomes (organ failure, readmission, and 100-day mortality)	0	3	1	1	3	0.8

(Early suspension), ED (Effective de-escalation), DD (Denial of de-escalation), DNC (De-escalation not considered), ID (Ineffective de-escalation), OXA-R (Oxacillin-resistant), ESBLs (Extended-spectrum beta-lactamase), ICU/SICU (Intensive Care Unit/Special Intensive Care Unit) (Intensive Care Unit), ANC (Absolute Neutrophil Count in cells/µL), and CRP (C-Reactive Protein)