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Some Routine Laboratory Measurements And Antibiotic Choice As Potential Predictors of Mortality in The Pediatric İntensive Care Unit: A Cross-Sectional Study

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Abstract

Aim: White blood cell (WBC), platelet (PLT) count, and CRP are some basic parameters to follow the outcome of patients in intensive care units. This study aimed to evaluate the differences in the outcome of patients related to some routine laboratory measurements and antibiotic preferences.

Methods: The participants of the study consisted of 179 pediatric ICU inpatients with gram-positive culture results. Hospital records covering the years 2016 to 2019 were reviewed. Other than the mortality status, data were collected on age, sex, the presence of fever, culture results, antibiotic preferences, and laboratory parameters such as WBC, PLT, and CRP levels.

Results: The median (IQR) age of the patients was 33.00 (8.00-66.00) months; 109 (60.89%) were boys, while 70 (39.11%) were girls. Of the patients, 90 (50.3%) had positive culture results, 59 (33%) received vancomycin, 31 (17.3%) received teicoplanin, and 34 (18.9%) had a fatal outcome. The cultured organisms were as follows: Staph. spp. (n=56, 31.3%), methicillin-resistant Staph. epidermidis (n=81, 45.3%), Staph. aureus (n=22, 12.3%), Staph. epidermidis (n=15, 8.4%), and methicillin-resistant Staph. aureus (n=5, 2.8%). WBC and PLT levels were higher in survived patients than the deceased ones ($p=0.001$ and $p<0.001$, respectively. There was no significant association of mortality and any of the studied categorical variables ($p>0.05$).

Conclusion: CRP and PLT are useful indicators for the diagnosis of serious bacterial infections and the prediction of the clinical outcome. There is no difference between using vancomycin or teicoplanin concerning mortality in the ICU.

Keywords: *WBC, platelet, CRP, pediatric intensive care unit, antibiotic therapy, Methicillin-resistant Staphylococcus aureus*

Introduction

Background/rationale

White blood cell (WBC) count is included in many scoring systems. For example, in an intensive care unit (ICU), low WBC in patients with sepsis suggests a bad prognosis (1). Also, thrombocytopenia is frequently seen in patients admitted to the ICU (2). Although many factors, including thrombin-mediated platelet activation, and complement activation may contribute low platelets (PLT), in the ICU, thrombocytopenia commonly indicates severe organ system problems and physiologic decompensation rather than primary hematologic issues (2).

On the other hand, CRP is a protein associated with nonspecific inflammation; it is produced in the liver and regulated by plasma interleukin-6. In cases of infection or damage to any organ system, the concentration of CRP will increase substantially (3). It was suggested that the most sensitive indicator for the diagnosis of neonatal sepsis in the pediatric intensive care unit is CRP (4).

Staphylococcus aureus causes life-threatening infection and commonly accompanies the clinical course of patients requiring intensive care. Staph. aureus infection in the ICU frequently reveals sepsis, ventilator-associated pneumonia, and infection of surgical sites or inserted medical devices (5).

Vancomycin and teicoplanin are effective antibiotics, especially used in the treatment of gram-positive infections; they are particularly useful in cases caused by methicillin-resistant Staphylococcus aureus (MRSA). Some advantages of the two antibiotics have been suggested, such as teicoplanin being less nephrotoxic than vancomycin (6).

Objectives

Changes in WCC, PLT, and CRP levels in patients in the intensive care unit were measured in this study to explore their relationship with the clinical outcome and mortality of patients in the ICU.

Methods

Study design

This is a retrospective cross-sectional study investigating hospital data. Study reporting was done per the STROBE guidelines (7).

Setting

The study was conducted at Marmara University School of Medicine, Department of Pediatrics, Division of Pediatric Critical Care. Patient data from 01.01.2016 to 01.01.2019 was retrieved from the hospital's repository.

Participants

Participants of the study consisted of pediatric ICU inpatients. During the study period, a total of 915 patients were admitted to the ICU. Of these, 180 with positive culture results were included in the study. One patient with some missing laboratory values was excluded (Figure 1).

Figure 1: Study flow diagram.

Variables

Data were collected from the hospital's electronic patient record system. The primary outcome variable of the study was mortality status (survived vs. deceased). Also, information for white blood cell count (WBC, microliter), platelet count (PLT, microliter), c-reactive protein levels (CRP, mg/L), presence of fever, culture source (blood vs. catheter), pathogen grown, and the type of antibiotics used were recorded.

As per the protocol of the ICU during the study period, patients with gram-positive culture results were clinically evaluated for fever, perfusion problems, pulses, capillary circulation time, and laboratory variables such as the trends in WBC and CRP, which resulted in the decision to implement antibiotics or not.

As a routine, venous blood was taken from all the subjects at the time of admission, placed into a vacuum tube containing anticoagulant, and then sent to the laboratory of Marmara University Hospital for the detection of WBC, PLT, and CRP levels. WBC and PLT values were analyzed by the LH780 automated hematology analyzer (Beckman Coulter, Brea, CA) using the volume-conductivity-light scatter technology. CRP level was measured by immunoturbidimetry. The analysis was performed with a Beckman Coulter AU5800 automatic biochemical analyzer (Beckman Coulter, Inc., Brea, CA, USA). The standard and reagents were provided by the manufacturer. All laboratory analyses were carried out following the manufacturer's instructions.

The cultures of catheters were done by the method described by Cleri et al. (8). Each catheter segment was taken to a 90-mm blood agar plate and rolled on the surface at least four times. Later, the catheter lumen was flushed with 2 ml of tryptic soy broth (TSB), which was diluted 10-fold, and 0.1 ml of each dilution was spotted onto horse blood agar plates. Finally, the whole segment was absorbed in 5 ml of TSB. Colonies were counted after 48-72 h of incubation. Coagulase-negative staphylococci were differentiated by the method described by Kloos and Smith (9). In the case of growth, antibiotic susceptibility work was performed with the disk diffusion method.

Blood cultures were collected in BacT/Alert (Biomérieux, Missouri, USA) aerobic and anaerobic blood culture bottles and placed in the automated microbial detection system. Cultures positive for coagulase-negative Staphylococcus, Propionibacterium, Micrococcus, Bacillus, and Corynebacterium, with detection in a single blood culture bottle and without clinical relevance, were considered as contaminants and were excluded.

Fever was defined as axillary temperature >38.5 ˚C lasting for more than one week.

Sample size

The sample size calculation was based on the main outcome variable, "mortality status." To detect a difference in the mortality ratio between 3 antibiotic status (No antibiotic/Vancomycin/Teicoplanin) using the Chi-square test with an effect size of 0.3 (medium), degree of freedom of 2, alpha error of 5%, and a power of 95%, a sample size of 172 cases are required (10).

Statistical methods

The data were analyzed with the Statistical Package for the Social Sciences (SPSS) version 25.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was performed to test if the numerical variables were normally distributed. The results were presented as frequencies, percentages, mean (±SD), median, and interquartile range (IQR). The Mann-Whitney U and Kruskal-Wallis tests were used to compare numerical variables, and the Chi-Square test was used for categorical variables. A p-value of <0.05 was considered statistically significant.

Results

Participants

Results for 179 participants were analyzed. The median (IQR) age of the patients was 33.00 (8.00-66.00) months. Of the patients, 109 (60.89%) were boys, while 70 (39.11%) were girls. Although the median age of the girls was slightly higher (37.50 months, min-max: 1-228 vs. 26.00 months, min-max: 2-201), this difference was not significant (Z=0.815, p=0.415).

Descriptive data

Of the patients, 90 (50.3%) had positive culture results, 59 (33%) received vancomycin, 31 (17.3%) received teicoplanin, and 34 (18.9%) had a fatal outcome.

The cultured organisms in decreasing order were as follows: Staph. spp. (n=56, 31.3%), methicillin-resistant Staph. epidermidis (n=81, 45.3%), Staph. aureus (n=22, 12.3%), Staph. epidermidis (n=15, 8.4%), and methicillin-resistant Staph. aureus (n=5, 2.8%).

Outcome data

There were no gender or fever differences concerning WBC, PLT, and CRP levels (Table 1). However, although there were no differences regarding WBC and PLT, patients with infection had higher CRP levels compared to those without infection (Table 1). On the other hand, WBC and PLT levels were higher in survived patients than the deceased ones (Table 1).

Table 1: Mean differences in WBC, PLT, and CRP levels compared to sex, fever, infection, and outcome groups

Variable	Group	Median (IQR)	Z*; p
WBC (/ml)	Male (n=109)	12900 (8900-17300)	Z=0.548, p=0.583
	Female (n=70)	11300 (7600-16700)	
	Culture + (n=90)	11700 (8300-17000)	Z=0.589, p=0.556
	Culture – (n=89)	12000 (9100-17300)	
PLT (/ml)	Male (n=109)	235000 (140000-378000)	Z=0.046, p=0.963
	Female (n=70)	233500 (169000-322000)	
	Culture + (n=90)	235000 (106000-3710000	Z=0.371, p=0.711
	Culture – (n=89)	233000 (158000-3510000	
CRP (mg/L)	Male (n=109)	23.3 (8-74)	Z=1.034, p=0.301
	Female (n=70)	39 (8-111)	
	Culture + (n=90)	43.5 (9.72-133)	Z=2.944, **p=0.003**
	Culture – (n=89)	16 (7-56)	
WBC (/ml)	Fever + (n=66)	12250 (8900-16100)	Z=0.115, p=0.908
	Fever – (n=113)	11700 (8300-17500)	
	Died (n=34)	7700 (5700-13500)	Z=3.460, **p=0.001**
	Survived (n=145)	12850 (9550-17350)	

PLT (/ml)	Fever + (n=66)	241500 (123000-395000)	Z=0.126, p=0.900
	Fever – (n=113)	233000 (167000-340000)	
	Died (n=34)	161500 (56000-232000)	Z=4.256, **p<0.001**
	Survived (n=145)	260000 (173000-394000)	
CRP (mg/L)	Fever + (n=66)	44.95 (9-97)	Z=1.653, p=0.098
	Fever – (n=113)	23 (7.28-65.7)	
	Dead (n=34)	32.1 (8-72)	Z=0.126, p=0.900
	Survived (n=145)	25.4 (8-79)	

*Mann-Whitney U test

There were no significant differences in WBC and PLT by the type of antibiotic given and the culture results. However, there were statistically significant differences in the CRP levels compared to the kind of used antibiotics; patients treated with teicoplanin had higher CRP levels. Also, the CRP levels were significantly different concerning the culture results; patients with Staph. aureus and methicillin-resistant Staph. aureus grown in the blood cultures had higher CRP levels (Table 2).

Table 2: Mean differences in WBC, PLT, and CRP levels compared to the administered antibiotics and blood culture groups

Variable	**Group**	**Median (IQR)**	**H*, p**
WBC (/ml)	No antibiotic	12000 (9100-17300)	H=1.807, p=0.405
	Vancomycin	10800 (6900-16300)	
	Teicoplanin	13200 (8500-19200)	
PLT (/ml)	No antibiotic	233000 (158000-351000)	H=0.503, p=0.778
	Vancomycin	240000 (158000-378000)	
	Teicoplanin	234000 (98000-371000)	
CRP (mg/L)	No antibiotic	16 (7-56)	H=8.976, **p=0.011**
	Vancomycin	34 (9-111)	
	Teicoplanin	48 (12-136)	
WBC (/ml)	Staph. epidermidis	10400 (6100-12600)	H=7.951, p=0.093
	Staph. aureus	13400 (10300-25800)	

	Methicillin resistant Staph. epidermidis	12900 (8900-17500)	
	Methicillin resistant Staph. aureus	12200 (8600-12900)	
	Staph. spp.	10700 (6650-15100)	
PLT (/ml)	Staph. epidermidis	176000 (123000-395000)	H=3.309, p=0.507
	Staph. aureus	208500 (104000-438000)	
	Methicillin resistant Staph. epidermidis	260000 (188000-378000)	
	Methicillin resistant Staph. aureus	234000 (158000-412000)	
	Staph. spp.	218000 (137500-317500)	
CRP (mg/L)	Staph. epidermidis	55 (23-175)	H=19.469, **p=0.001**
	Staph. aureus	68.5 (26-186)	
	Methicillin resistant Staph. epidermidis	14.3 (7.37-52.8)	
	Methicillin resistant Staph. aureus	105 (5-133)	
	Staph. spp.	21.15 (7.27-66.8)	

*Kruskal-Wallis test

There were no relationships among mortality or clinical outcome, gender, fever, infection, the type of used antibiotic, and the place and result of culture (Table 3).

Table 3: The relationships of clinical outcome (mortality) and other categorical variables

	Died	**Survived**		
	n (%)	**n (%)**	**χ^2**	**p**
Boys	25 (73.5)	83 (57.2)	2.911	0.088
Girls	9 (26.5)	62 (42.8		
With fever	14 (41.2)	52 (35.8)	0.302	0.582
Without fever	20 (58.8)	93 (64.2)		
No antibiotic	14(41.2)	75 (51.7)	1.152	0.562
Vancomycin	13 (38.2)	46 (31.7)		
Teicoplanin	7 (20.6)	24 (16.6)		

Staph. epidermidis	3 (8.8)	12 (8.3)	5.155	0.272
Staph. Aureus	5 (14.7)	17 (11.7)		
MR Staph. epidermidis	11 (32.4)	70 (48.3)		
MR Staph. aureus	0 (0)	5 (3.4)		
Staph. spp.	15 (44.1)	41 (28.3)		

MR: methicillin-resistant.

Discussion

Key results

The patients with infection had higher CRP levels than in patients without infection. WBC and PLT levels were higher among survivors compared to the deceased patients. On the other hand, patients treated with teicoplanin and patients whose blood cultures grew Staph. aureus or methicillin-resistant Staph. aureus had higher CRP levels.

Limitations

A noteworthy limitation of this study is its retrospective nature. The study was based on the clinical protocol of the ICU during the study period, where the decision on implementing antibiotics and which antibiotic to start depended on the clinical judgment of the clinician in charge. On the other hand, including some other variables such as the mean platelet volume, platelet distribution width, platelet count, and platelet crit could yield extra information.

Interpretation

Since clinical manifestations of most febrile infants are nonspecific, differentiation of serious bacterial infections from self-limiting viral illnesses is a major challenge (11). Many studies were performed to identify potential screening markers to assist physicians reliably discriminating children with fever and increased risk of bacterial infection from children with lower risk. One of these indicators is CRP, an acute-phase reactant that rapidly increases during infection, inflammation, and trauma (12). The results of the present study indicate that CRP is still an essential criterion for bacterial infection in children in the ICU. In a recent survey, it has been claimed that CRP is a useful biomarker in predicting serious bacterial infections in young febrile infants (11).

It has been reported that neonates with early-onset sepsis had a significantly higher WBC count than neonates without sepsis. This remained significant even after 12-24 hours of admission (13). In the present study, WBC levels showed no relationship with sex, fever, infection, antibiotic type, culture results, or mortality. In a related study, the authors concluded that WBC count by itself was neither a dependable nor accurate predictor of severe bacterial infection in febrile infants (14). The findings of another study confirm this suggestion (11).

A recent study investigated the role of platelets (15). In sepsis, platelets facilitate the development of hyper inflammation, disseminated intravascular coagulation, and micro thrombosis, and subsequently may lead to multiple organ failure. Incongruous accumulation and activity of platelets are crucial events in the development of sepsis-related complications such as acute lung and kidney injury. In the present study, WBC and PLT levels were higher in surviving patients than in the deceased ones. Low PLT in children who died in the pediatric ICU may be related to hyperinflammation due to the excessive platelet activation. Thus, low PLT in these patients may be related to increased platelet consumption, increased platelet destruction (immune mechanisms) (16), and increased platelet sequestration (17). Also, in a

case-control study, the mean platelet volume, platelet distribution width, platelet count, and platelet crit were suggested as predictors of in-hospital pediatric mortality (1).

Suitable antimicrobial therapy is a prerequisite for appropriate patient outcomes. Incorrect or suboptimal use of antibiotics can lead to many undesirable issues, such as increased length of stay, resistant infections, and mortality (18). Critically ill intensive care patients, especially those with severe sepsis, are at risk of antibiotic failure and secondary infections associated with inappropriate antibiotic use. The common ICU infections can only be handled via the initiation of empiric antibiotic therapy based upon local susceptibilities, following by daily evaluation of signs and symptoms of the infection, and narrowing of antibiotic therapy when possible.

MRSA is a widespread cause of bloodstream and other invasive infections (19). Since a long time, vancomycin is the drug of choice for the treatment of these cases. However, one of the chief limitations for the use of vancomycin is its potential to cause nephrotoxicity (20). Teicoplanin, another glycopeptide, has basically the same efficacy of vancomycin with some advantages such as once-daily bolus administration, intramuscular use, lack of requirement for routine serum monitoring, and possibly less nephrotoxicity (21). On the other hand, teicoplanin is expensive compared to vancomycin.

Vancomycin and teicoplanin are the two commonly-used agents to treat gram-positive infections. They are especially employed in infections caused by MRSA. There is uncertainty regarding the effects of teicoplanin compared to vancomycin on the kidney functions; some previous studies suggested that teicoplanin is less nephrotoxic than vancomycin (6). In the present study, the patients treated with teicoplanin had higher CRP levels, but there was no relationship between the type of antibiotic and mortality. Also, in a meta-analysis, no difference was found between vancomycin and teicoplanin concerning clinical or bacteriological response (22).

Conclusion

The results of the present study demonstrate that CRP is still the most sensitive indicator for the diagnosis of neonatal infection as well as sepsis in pediatric intensive care units; it may be also valuable for predicting the clinical outcome. Besides, PLT is a crucial indicator to follow the clinical outcome in children in the ICU. Low PLT in children of bad prognosis may be related to hyper inflammation due to the excessive platelet activation, then, increased platelet consumption, increased platelet destruction, and increased platelet sequestration. Additionally, there is no difference in treating severe bacterial infections in the ICU with vancomycin or teicoplanin regarding the clinical outcome.

Conflict of Interest

The authors have no conflict of interest in this study.

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References

1. *Waheed U, Williams P, Brett S et al. White cell count and intensive care unit outcome. Anaesthesia. 2003 Feb;58(2):180–2.*
2. *Zarychanski R, Houston DS. Assessing thrombocytopenia in the intensive care unit: the past, present, and future. Hematol Am Soc Hematol Educ Progr. 2017 Dec;2017(1):660–6.*
3. *Gao L, Liu X, Zhang D et al. Early diagnosis of bacterial infection in patients with septicopyemia by laboratory analysis of PCT, CRP and IL-6. Exp Ther Med. 2017 Jun;13(6):3479–83.*
4. *Li Z, Wang H, Liu J et al. Serum soluble triggering receptor expressed on myeloid cells-1 and procalcitonin can reflect sepsis severity and predict prognosis: a prospective cohort study. Mediators Inflamm. 2014;2014:641039.*
5. *Sampedro GR, Bubeck Wardenburg J. Staphylococcus aureus in the Intensive Care Unit: Are These Golden Grapes Ripe for a New Approach? J Infect Dis. 2017 Feb;215(suppl_1):S64–70.*
6. *Cavalcanti AB, Goncalves AR, Almeida CS et al. Teicoplanin versus vancomycin for proven or suspected infection. Cochrane database Syst Rev. 2010 Jun;(6):CD007022.*
7. *von Elm E, Altman DG, Egger M et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014 Dec;12(12):1495–9.*
8. *Cleri DJ, Corrado ML, Seligman SJ. Quantitative culture of intravenous catheters and other intravascular inserts. J Infect Dis. 1980;141(6):781–6.*
9. *Kloos WE, Bannerman TL. Manual of clinical microbiology. Am Soc Microbiol Washington, DC. 1991;*
10. *Faul F, Erdfelder E, Lang A-G et al. Power 3:A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;*
11. *Zarkesh M, Sedaghat F, Heidarzadeh A et al. Diagnostic value of IL-6, CRP, WBC, and absolute neutrophil count to predict serious bacterial infection in febrile infants. Acta Med Iran. 2015 Jul;53(7):408–11.*
12. *Hsiao AL, Baker MD. Fever in the new millennium: a review of recent studies of markers of serious bacterial infection in febrile children. Curr Opin Pediatr. 2005 Feb;17(1):56–61.*
13. *Abdollahi A, Shoar S, Nayyeri F et al. Diagnostic Value of Simultaneous Measurement of Procalcitonin, Interleukin-6 and hs-CRP in Prediction of Early-Onset Neonatal Sepsis. Mediterr J Hematol Infect Dis. 2012;4(1):e2012028.*
14. *Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. Pediatrics. 2001 Aug;108(2):311–6.*
15. *de Stoppelaar SF, van 't Veer C, van der Poll T. The role of platelets in sepsis. Thromb Haemost. 2014 Oct;112(4):666–77.*
16. *Ghosh TK, Khan N, Malik A. Platelet auto-antibodies in septicaemic patients. Indian J Pathol Microbiol. 1999 Jan;42(1):31–5.*
17. *Greinacher A, Selleng K. Thrombocytopenia in the intensive care unit patient. Hematol Am Soc Hematol Educ Progr. 2010;2010:135–43.*
18. *Campion M, Scully G. Antibiotic Use in the Intensive Care Unit: Optimization and De-Escalation. J Intensive Care Med. 2018 Dec;33(12):647–55.*
19. *Bubacz MR. Community-acquired methicillin-resistant Staphylococcus aureus: an ever-emerging epidemic. AAOHN J. 2007 May;55(5):193–4.*
20. *Maclayton DO, Hall RG 2nd. Pharmacologic treatment options for nosocomial pneumonia involving methicillin-resistant Staphylococcus aureus. Ann Pharmacother. 2007 Feb;41(2):235–44.*
21. *Wood MJ. Comparative safety of teicoplanin and vancomycin. J Chemother. 2000 Nov;12 Suppl 5:21–5.*
22. *Wood MJ. The comparative efficacy and safety of teicoplanin and vancomycin. J Antimicrob Chemother. 1996 Feb;37(2):209–22.*