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Newer Parameters on Electronic Cell Counter for Diagnosis of Infections

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Review Article

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Abstract

Blood stream infection (BSI) and sepsis are life threatening conditions and early identification of pathogen with prompt intervention is important for patient management. Need for early diagnosis of sepsis has incredibly boosted the research for innovative biomarkers. The cellular and morphological characterization of cells is an indispensable part of hematology workup. The automated hematology analyzers are being routinely used for total cell counts and differential leukocyte analysis. But technological advancements in automated hematology analyzers have paved the way for many additional parameters which are capable of providing extended information to help clinicians and laboratory professionals. This review emphasizes the application of additional innovative parameters reported by modern hematology analyzers as a tool for early recognition of sepsis with impact on clinical practice.

Keywords: Automated Cell Counters; Volume Conductivity and Scatter Parameter; Cell Population Data; Sepsis

Abbreviations: BSI: Blood Stream Infection; ANC: Absolute Neutrophil Count; CPD: Cell Population Data; VCS: Conductivity and Scatter; MNV: Mean Neutrophil Volume; MMV: Mean Monocyte Volume; IGs: Immature Granulocytes; FDA: Food and Drug Administration.

Introduction

Bloodstream infections (BSIs) are perpetual in ICU patients and are a prognostic factor for severe sepsis [1]. There is manifold risk for BSI patients to develop sepsis, hence early diagnosis of bacteremia is key to provide early and aggressive management in order to improve outcomes [2]. Active screening in critically ill patients is required to predict the risk of developing sepsis, which continues to be one of the substantial causes of morbidity and mortality in critically ill patients of any age. However, the timely diagnosis of sepsis still remains a continuing challenge in clinical practice [3]. There is growing attention among researchers about innovative hematological parameters in sepsis, which can be employed either as a diagnostic biomarker or for therapeutic monitoring [4]. Presently hematology analyzer cater a wide spectrum of traditional and additional innovative parameters. Historically, complete blood count, peripheral blood mear examination and blood culture have been the mainstay of diagnosing sepsis.Increase in WBC count, absolute neutrophil count (ANC), immature/ total neutrophil ratio, shift to left in peripheral blood smear have been used as an indicators of bacterial infections [5]. In addition, characteristic morphological changes in neutrophils like toxic granulation, cytoplasmic vacuolation and occasional Dohle bodies are also evident in sepsis [6]. However, relying on manual examination of peripheral smears is more labor intensive, imprecise, time consuming and requires technical expertise in hematology.

Automation in hematology has markedly enhanced the speed, efficiency, reproducibility and high accuracy of blood analysis. Modern hematology cell counters are rendering five to seven parts differentialwhite cell analysis using different

technologies like optical methods, fluorescent flow cytometry, radiofrequency conductivity, impedance based technology with an underlying Coulter principle or a combination of the above methods [7]. Recent technological evolution in the automated hematology analyzers has led to inception of many novel parameters to characterize and specify the blood cells. Many of such parameters provide a potential means to improve the screening, prediction and detection of infections. The use of additional parameters provided by sophisticated hematology analyzers for a number of clinical applications has been increased substantially [8]. These parameters are derived during automated differential analysis without requirement of additional specimen and can be measured or calculated. The following section discusses some of these additional innovative parameters in brief.

Cell Population Data

In recent times, there has been a fundamental change in practice of reporting CBC parameters along with exploration of the cell population data (CPD) - data generated from Volume, Conductivity and scatter (VCS) technology in detecting various hematologic and non-hematologic conditions. VCS technology is the most dynamic tool available for blood cell analysis offering the greatest sensitivity, specificity and efficiency of any blood cell analysis system available today [9] Volume (V) and size of cell is quantified using direct current impedance (Coulter Principle) to physically measure the volume that the entire cell displaces in an isotonic diluent resulting in accurate measurement of all cell types regardless of their orientation in the light path. Conductivity (C) and light scatter (S) is derived using radiofrequency opacity and laser beam to characterize the internal structure of the cell including chemical composition and nuclear volume. VCS is the only single channel analysis that uses three independent energy sources to probe > 8000 WBC's in a few seconds in their near native state following lysis of RBC's generating quantitative, more objective and reproducible data as compared to manual differential count without requirement of additional sample [10]. Celik, et al. [11] studied neutrophil VCS parameter in diagnosing sepsis in 76 culture positive neonates and found with a sensitivity of 79% and specificity of 82%. They suggested to use in combination of CRP, the mean and SD of neutrophil volume and interleukin-6 (IL-6) levels for screening method for sepsis. Mardi, et al. [12] studied neutrophil and monocyte VCS parameter in adult patients with sepsis and found MNV (mean neutrophil volume) and MMV (mean monocyte volume) taken together to have diagnostic potential in discriminating sepsis with non- systematic infections and controls. Numerous other studies have reported the data from VCS technology analyzers provides a comparable reflection of cell morphology [13,14].

CPD is often referred as "Investigation screen parameters" and has a potential in diagnosing and anticipating likelihood of a variety of infections like malaria, dengue, viral infections, bacterial infections and sepsis as it provides quantitative assessment on morphological and functional characteristics of leukocytes. The variation of CPD in response to stimuli like infections, offers rapid information on leucocyte activation and functional activity, improving early diagnosis of sepsis [15]. Thus, combining leukocyte parameters outlining both numerical and morphological information will help to better differentiate activation of cells. However, lack of standardization of these newly evolved parameters also poses a limitation of their use in clinical decisions [16].

Immature Granulocytes (IGs)

IGs characterize and quantify an immature myeloid cell which elaborates promyelocytes, myelocytes and metamyelocytes that are released from bone marrow during infection, inflammation and sepsis [17]. The presence of IGs in peripheral blood denotes leukopoiesis and considered to be earliest indicator of bone marrow stimulation. Conventionally IG in the circulating blood is often considered as a clinical indicator of infection or inflammation. But, the manual differential count on peripheral blood is more imprecise, subjective with wide interobserver variability and poor reproducibility particularly in leucopenic patients [18]. With the advent of modern autoanalyzer it is possible to count IGs efficiently without need of additional sampling, with more precise characterization of immature granulocytes resulting in accurate measurements in patients with infections [19]. Several studies have proven the utility of IG percentage and count as a potential marker to predict the severity of infection and precluding the use of IG count as a screening test for sepsis [20,21]. Deviation from normal values of the mean and SD of neutrophil volume can predict sepsis with an indication towards acute bacterial infections [22].

Malaria Diagnosis

Hematological changes are among the most frequent complications occurring in malaria [23]. Early prediction of the hematological changes facilitates the clinicians to accomplish early therapeutic intervention to prevent the occurrence of major complication. There is a continuous search for alternative methods to detect and quantify malaria parasites beside microscopy and immunochromatographic tests. The most studied malaria related hematological abnormality in autoanalyzer is the presence of hemozoin containing monocyte and granulocyte which results in atypical scattergrams generated during complete blood count of malaria -infected blood sample. Birefringent depolarizing malaria pigment is ingested by monocyte and granulocytes, altering the light scatter properties of WBC's resulting in unusual light scatter pattern. Cell Dyn (CD) - 3500 was

the first autoanalyzer to detect malaria by characterizing hemozoin containing leucocytes especially monocytes by employing laser light scatter at various angles resulting in multiple angle polarized scatter separation for WBC analysis [24]. Intra-erythrocytic haemozoin has been identified using flow cytometry principal, however it has low sensitivity for detection of P.falciparum as the circulating ring forms of the parasite carry minimal amounts of haemozoin [25]. Briggs, et al. & Jain, et al. [26,27] suggested the use of Standard deviation volume of monocytes and lymphocyte to flag for the likely presence of parasites of malaria in infected patients. Increased volumes leading to SD of the volumes occur due to reactive changes in cell size of lymphocytes and monocytes. The authors calculated and proposed an algorithm called as malaria factor by combining these changes as an indicator of malarial infection. They documented a cut-off value for the Malaria Factor of more than 3.7, the specificity of which was 94% and sensitivity was 98%. Automated enumeration of malaria parasitemia still needs validation by microscopy, however modern autoanalyzers should certainly be considered as adjunctive diagnostic tool for detection of unsuspected cases.

Other Parameter

Sepsis causes activation of monocytes, this infection related variation in size is monitored by measuring the spread of monocytes in coulter chambers. Food and Drug Administration (FDA) recently approved the Monocyte Distribution Width (MDW) as a parameter to improve the early detection of sepsis, available as a part of complete blood count with differential [28]. Crouser, et al. [29] observed the 83.0% sensitivity of MDW, which was higher than other biomarkers like CRP (69.7%) and PCT (76.6 %) and have shown that normal MDW combined with clinical scores like SIRS or qSOFA reduced the probability of sepsis. MDW is a valuable tool in discriminating sepsis and all other conditions. Many studies have suggested MDW as a complimentary marker to clinical sepsis in early detection of sepsis and may be considered as a fifth SIRS or fourth qSOFA criteria to improve the accuracy of sepsis diagnosis [30,31]. Although many of the above discussed additional parameters are still in research mode but the preliminary data obtained in many studies is very promising. These clinical benefits can be real. Despite these triumphs, the routine use of many parameters has not yet arrived.

Salient Points

- High throughput labs require automation of their hematology workflow.
- VCS parameters can be a cardinal diagnostic aid in early diagnosis of sepsis.
- VCS parameters can be used as a sensitive indicator for detecting infections when the WBC count is within normal limits.
- These morphological parameters are promptly obtained from modern analyzers with advantage of being more objective, accurate and cost- effective.
- Plethora of other clinical applications of the VCS technology still merits further exploration.

Conclusion

Over the past decade, automated hematology analyzers have undergone tremendous technical advancement expanding the range of reportable parameters allowing accessibility to more cellular information as compared to simple routine CBC with differential. This added information can be utilized to evolve the traditional concept of laboratory hematology to produce deeper clinical insights to bring better patient care and more options for laboratory professionals. Both laboratory physicians and clinicians must acknowledge the abilities and limitations of these analyzers and need to keep up to date with these advances. These innovative additional parameters can be considered as an early, inexpensive and widely available tool for prediction of infections allowing timely management of patient. Additional integration of such parameters in clinical practice may lead to more reliable results that are clinically useful and provides an added value.

References

1. Laupland KB (2013) Incidence of Bloodstream Infection: A Review of Population-Based Studies. Clin Microbiol Infect 19(6): 492-500.
2. Timsit JF, Laupland KB (2012) Update on Bloodstream Infections in ICUs. Curr Opin Crit Care 18(5): 479-486.
3. Vincent JL (2016) The Clinical Challenge of Sepsis Identification and Monitoring. PLos Med 13(5): E1002022.
4. Manucha V, Rusia U, Sikka M, Faridi MMA, Madan N, et al. (2002) Utility Of Haematological Parameters And C-reactive Protein in the Detection of neonatal sepsis. J Paediatr Child Health 38(5): 459-464.
5. Wile MJ, Homer LD, Gaehler S, Phillips S, Millan J (2001) Manual Differential Cell Counts Help Predict Bacterial Infection. A Multivariate analysis. Am J Clin Pathol 115(5): 644-649.
6. Osrin D, Vergnano S, Costello A (2004) Serious Bacterial Infections in newborn infants in developing countries. Curr Opin Infect Dis 17(3): 217-224.
7. Green R, Sebastian WH (2015) Development, History, and Future of Automated Cell Counters. Clin Lab Med

35(1): 1-10.

8. Hoffmann HJ (2019) New Hematology Analyzer Parameters and their clinical significance. Eflm Newsl 1: 1-36.
9. Purohit AHL, Kumar P, Sharma S, Kapil A, Gupta A, et al. (2015) Volume, conductivity, and scatter Parameters as diagnostic aid to bacterial sepsis: A Tertiary Care Experience. Indian J Pathol Microbiol 58(4): 459-463.
10. Chaves F, Tierno B, Xu D (2006) neutrophil volume distribution width: a new automated hematologic parameter for acute infection. Arch Pathol Lab Med 130(3): 378-380.
11. Celik IH, Demirel G, Sukhachev D, Erdeve O, Dilmen U (2013) Neutrophil volume, conductivity and scatter parameters with effective modeling of molecular activity statistical program gives better results in neonatal sepsis. Int J Lab Hematol 35(1): 82-87.
12. Mardi D, Fwity B, Lobmann R, Ambrosch A (2010) Mean cell volume of neutrophils and monocytes compared with c - reactive protein, interleukin-6 and white blood cell count for prediction of sepsis and nonsystemic bacterial infections. Int J Lab Hematol 32(4): 410-418.
13. Celik IH, Demirel G, Aksoy HT,Erdeve O, Tuncer E, et al. (2012) Automated determination of neutrophil vcs parameters in diagnosis and treatment efficacy of neonatal sepsis. Pediatr Res 71(1): 121-125.
14. Urrechaga E, Bóveda O, Aguirre U (2019) Improvement in detecting sepsis using leukocyte cell population data (CPD). Clin Chem Lab Med 57(6): 918-926.
15. Park SH, Park CJ, Lee BR, Nam KS, Kim MJ, et al. (2015) Sepsis affects most routine and cell population data (CPD) obtained using the Sysmex XN-2000 blood cell analyzer: neutrophil-related CPD NE-SFL and NE-WY provide useful information for detecting sepsis. Int J Lab Hematol 37: 190-198.
16. Chhabra G (2018) Automated hematology analyzers: recent trends and applications. J Lab Physicians 10(1): 15-16.
17. Cornbleet PJ (2002) Clinical utility of the band count. Clin Lab Med 22(1): 101-136.
18. Arderiu XF, Panyella MG, Bach DD (2007) Between-examiner reproducibility in manual differential leukocyte counting. Accred Qual Assur 12: 643-645.
19. Senthilnayagam B, Kumar T, Sukumaran J, Jeya M, Ramesh RK (2012) Automated measurement of immature granulocytes. Performance characteristics and utility in routine clinical practice. Pathol Res Int pp: 483670.
20. Lari MAA, Kickler TS, Borowitz MJ (2003) Immature granulocyte measurement using the sysmex xe-2100: relationship to infection and sepsis. Am J Clin Pathol 120(5): 795-799.
21. Ünal Y, Barlas Am (2019) Role of increased immature granulocyte percentage in the early prediction of acute necrotizing pancreatitis. Ulus Travma Ve Acil Cerrahi Derg 25(2): 177-182.
22. Bagdasaryan R, Zhou Z, Tierno B, Rosenman D, Xu D (2007) Neutrophil VCS parameters are superior indicators for acute infection. Lab Hematol 13(1): 12-16.
23. Abro AH, Ustadi AM, Younis NJ, Abdou AS, Hamed DA, et al. (2008) Malaria and Hematological Changes. Pak J Med Sci 24(2): 287-291.
24. Wever PC, Henskens YM, Kager PA, Dankert J, Gool TV (2002) Detection of imported malaria with the cell-dyn 4000 hematology analyzer. J Clin Microbiol 40(12): 4729-4731.
25. Rebelo M, Shapiro HM, Amaral T, Cristino JM, Hänscheid T (2012) Haemozoin detection in infected erythrocytes for *Plasmodium falciparum* malaria diagnosis - prospects and limitations. Acta Trop 123(1): 58-61.
26. Briggs C, Da Costa A, Freeman L, Aucamp L, Ngubeni B, et al. (2006) Development of an automated malaria discriminant factor using VCS technology. Am J Clin Pathol 126(5): 691-698.
27. Jain M, Gupta S, Jain J, Grover RK (2012) Usefulness of automated cell counter in detection of malaria in a cancer set up-our experience. Indian J Pathol Microbiol 55(4): 467-473.
28. Crouser ED, Parrillo JE, Seymour C, Angus DC, Bicking K, et al. (2017) Improved early detection of sepsis in the ED with a novel monocyte distribution width biomarker. Chest 152(3): 518-526.
29. Crouser ED, Parrillo JE, Martin GS, Huang DT, Hausfater P, et al. (2020) Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA. J Intensive Care pp 8: 33.
30. Woo AL, Oh Dk, Park CJ, Hong SB (2021) Monocyte distribution width compared with C- reactiveprotein and procalcitonin for early sepsis detection in the emergency department. PLos One 16(4): e0250101.
31. Agnello L, Bivona G, Vidali M, Scazzone C, Giglio RV, et al. (2020) Monocyte distribution width (MDW) as a screening tool for sepsis in the emergency department. Clin Chem Lab Med 58(11): 1951-1957.