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monocytes, but with lower expression of HLA- DR in peripheral blood of septic patients.[29]

A study done by Paknezhad et.al. (2018) of 30 severely septic patients admitted in the ICU, found lower HLA- DR expression in non- survivors versus survivors of sepsis.[30]

Others found a lower HLA- DR level in septic neonates and found a prognostic value for HLA- DR in this group of patients.[31]

The Area under the curve (ROC curve) for HLADR in our study was 0.856. A cut off value of 1.960 was postulated for best sensitivity and specificity (73% sensitivity and 84% specificity).

As diagnosing sepsis is a difficult task, people often use multiple parameters simultaneously; that is why it is best, if we use CD64 and HLA DR together and thus, a Sepsis Index is created (SI). In our study, SI was an effective tool of predicting sepsis. The area under the curve equals 0.798 with a 91% cut off value decided which corresponds to 65% sensitivity and 80% specificity. The mean SI in controls is 74% while in probable sepsis is 105% while in proven sepsis is 180%.

The study by Chauhan et.al. (2017) indicates that the diagnosis of sepsis is better through the combination of nCD64 and mHLA- DR (innate immunity markers) for better treatment to improve the prognosis of these patients. Thus, this study can help to improve the decision making process of management. An advanced technique such as flow cytometry is undeniably the best tool for analyzing cell- cell interaction, signaling process, surface markers, proliferation and differentiation, protein secreted by cells, and intracellular molecules. In this study, the cell surface markers nCD64 and mHLA- DR are used to find out the SI with respect to the cut off range of healthy controls.[32]

In a study by Pradhan et.al. (2016), expression of nCD64 was significantly high in the infected group while mHLA- DR was significantly low as compared to the non- infected group and healthy controls.[33]

**Conclusion& Recommendations:**

1. HLA DR MFI was proven to drop significantly in neonates with neonatal sepsis.
2. CD64 doesn't show a significant role in diagnosing early neonatal sepsis.
3. Other hematological tests such as CRP and TLC help in diagnosing and following sepsis.
4. A combination of markers like CRP, HLA DR, Sepsis Index have to be assesses together for prediction of early neonatal sepsis.
5. HLA DR is the most specific marker followed by the SI.

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In SI there is significance between SI and sepsis between control, probable and proven sepsis (0.0001).

Table (2) Suggested cut off value of HLA DR MFI in different patients with sepsis from healthy controls with their sensitivity and specificity

| | Sensitivity | Specificity |
|---|---|---|
| 1.555 (Highest specificity) | 52.2% | 96% |
| 1.960 (Cut off value) | 73% | 84% |
| 2.315 (Highest sensitivity) | 91.3% | 32% |

Regarding, HLA DR MFI, 1.960 is considered the cut off point as it has 73% sensitivity and 84% specificity, which are considered the best values for both.

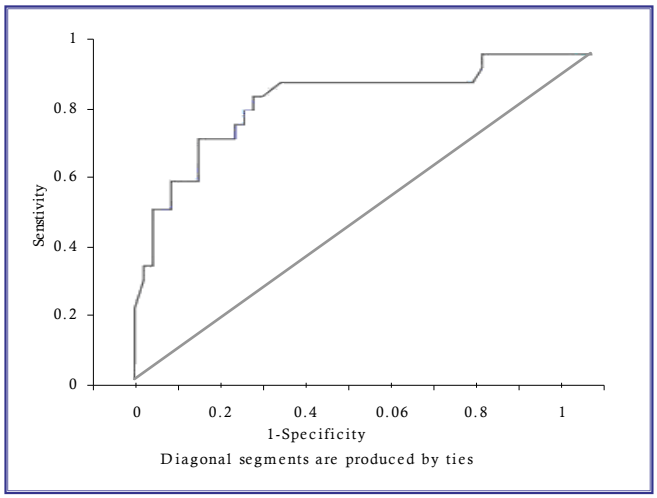



Figure (2) ROC curve of HLADR MFI (L) in proven sepsis.

**Discussion:**

In this study, 50 cases were enrolled from the NICUs of El Galaa Teaching Hospital and Cairo University. They are sub grouped into 23 cases proven to have neonatal sepsis (positive blood culture) and 27 cases addressed as probable sepsis due to the presence of signs of sepsis but with negative blood cultures; These are compared to 50 healthy neonates (control group).

In our study, the most common organisms isolated in septic patients were Klebsiella (60.9%), E.coli (26.1%), Pseudomonas (4.3%), MRSA (4.3%), Candida (4.3%). Similarly, the study by Abdul Halim et.al. found that the most common organisms were CONS (45%), where Gram negative bacilli including E. Coli, Klebsiella and Enterobacter species represented 18% of the microorganisms.[14]

Due to the variability of results, it is evident that the causative organism varies from NICU to NICU, between geographical areas and in the same area according to time. That is why the infection control of each hospital must adjust their antibiotics accordingly.

Regarding hematological tests, a high significant difference was detected between cases and controls as regards TLC and CRP in this study. This is in concordance with several studies which found that sepsis episodes were characterized by significant high white blood cell counts, immature/ total neutrophil ratios and low platelet counts compared to the non- septic groups.[15]

Regarding CRP, in our study the mean CRP is 3 (mg/L) in the control group, 11.42 (mg/L) in probable sepsis and 67.83 (mg/L) in proven sepsis; so we can say that its measurement is of significant value.

A previous postulated that CRP is produced within six to eight hours of exposure to an infection or tissue damage. It has a half- life of 19 hours and may increase more than 1000- fold during an acute phase response.[16]

Regarding CD64 in this study, the mean CD64 expression in neonates with sepsis was insignificant when compared to the control and probable sepsis groups.

This agrees with a meta- analysis by Shi et.al. (2016) that did not find CD64 a sensitive or a specific marker for sepsis.[17]

The hematologic scoring system assigns one score for each of the seven indices (abnormal total leukocyte count, abnormal total neutrophil (PMN) count, elevated immature PMN count, elevated immature to total PMN ratio, Immature to mature PMN ratio $\geq 0.3$, platelet count $\leq$ 150.000/mm3, and pronounced degenerative changes in PMNs) with higher scores indicating greater incidence for sepsis.[17] A previous report showed that abnormal neutrophil counts at the time of disease are only observed in two thirds of infants, so the neutrophil count does not provide an adequate confirmation of sepsis.[18] On the contrary, many studies showed a rise in the percentage of CD64 in the proven sepsis groups.[19][20] Also, similar results are seen in a study by Garcia et.al. (2013) revealing that patients with sepsis had a greater number of circulating CD64 positive PMNLS (mean 71%) than in controls (mean 19%).[21]

CD64 is shown to have a significant correlation with CRP level, which is a laboratory marker of neonatal sepsis pointing to its usefulness as an additional marker of sepsis.[22]

This is in agreement with many previous studies that found that CD64 correlates with CRP.[23] and proved by many others to have a higher discriminating power than CRP.[24] Furthermore, Al-Taee (2016) claims that CD64 has 85.9% sensitivity and 78.1% specificity for sepsis.[22]

Another study by Tang et.al. (2018) also states that the CD64 indices of the sepsis and non- sepsis groups were significantly higher than those of the control group. Therefore, it can be used for the early and rapid diagnosis of neonatal sepsis. However, there was no difference between the probable and proven sepsis, this might be because the expression levels of CD64 in the neutrophils were not elevated for a long time.[25]

In another study by Saiful et.al. (2014), neutrophil CD64 showed high sensitivity 100% and specificity 54.9%. Specificity was low in this study because of the large number of false positive results. This may be due to the small sample size and the blood culture was positive for only 22.5% cases of neonatal sepsis.[26]

Contrary to our results, Elawady et.al. (2014) found that CD64 had the highest sensitivity (96%), specificity (100%), PPV (96.2%), and NPV (100%), with cutoff values of 45.8%.[27]

Another result showed that neutrophil CD64 has sensitivity, specificity, PPV and NPV of 100%, 30%, 68.2% and 100% respectively. Choo et.al. (2012) reported a sensitivity of 91% and specificity of 83%.[28]

Regarding HLA DR, it has shown positive significance with the possibility of occurrence of sepsis.

A research by Winkler et.al. (2017) found a higher number of

3. The clinical criteria taken as indicative of sepsis were:
   a. Maternal risk factor such as fever, prolonged rupture of amniotic membrane >24 hr and chorioamnitis.
   b. Neonatal history: low birth weight (<2500 grams), premature birth (<37 weeks) and full term neonates.
   c. Signs and symptoms of sepsis: feeding intolerance, lethargy, temperature instability, apnea, respiratory distress, poor perfusion, seizures, tachypnea, bradycardia, abdominal distension or vomits.

   Group I (Proven Sepsis): It consisted of 23 newborn infants (full- term and preterm) with obvious clinical signs of infection and positive bacterial blood culture, Their gestational age ranged from (36- 39) wks., their age ranged from (1- 28) days, their weight ranged from (1- 3.5) kg, their sex is: 11 are females and 12 are males; 20 of them were born by caesarian section, 3 were born by normal vaginal delivery.

   Group II (Probable Sepsis): Included 27 neonates (full- term and preterm) with negative bacterial culture but have three or more clinical signs of infection such as fever, temperature instability, tachycardia, tachypnea, abdominal distention, respiratory distress, seizures, apnea, cyanosis, oliguria, gastrointestinal bleeding or petechiae. Their gestational age ranged from (36- 39) weeks, their age ranged from (1- 28) days, their weight ranged from (1- 3.5) kg; 17 were males and 10 females, 4 of them were born by normal vaginal delivery and 23 by caesarian section.

   Group III (Control Group): Included 50 neonates were enrolled in this study as a control group during their attendance for usual routine assessment, all considered as healthy neonates with matched gestational age, age and weight as control group (female and male). They were under investigation because of a suspicion of different diseases, but all had normal results and no illness was subsequently.

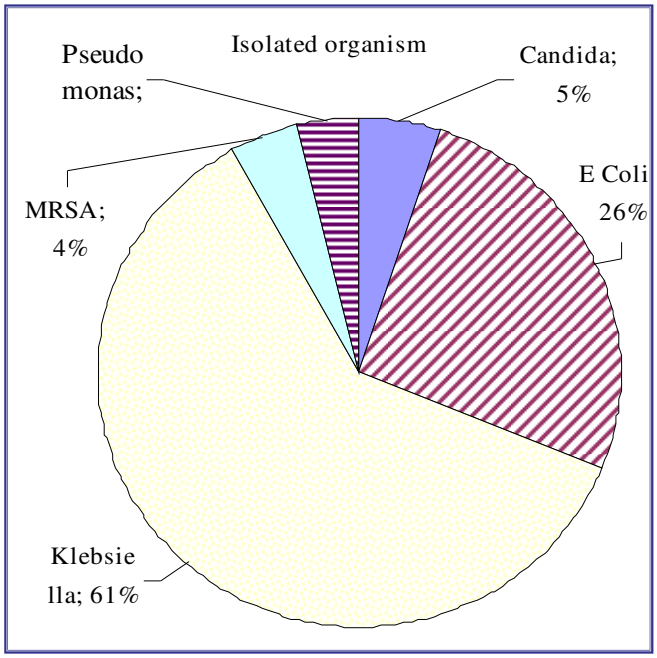
   Before initiation of antibiotic therapy in infants suspected of sepsis, blood samples for blood culture (1ml), flow cytometry analysis (2ml) were obtained by peripheral venous puncture.
4. Hematological Tests: Total leukocyte count, CRP and platelet count were done for each neonate. Abnormal values of these tests (white blood cell count< 4000 or> 15000 $mm^3$, platelet< 150.000 and CRP> 6) were considered as supportive for diagnosis of sepsis.

**Statistical Methods:**

Accuracy was represented using the terms sensitivity, and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers in diagnosing sepsis. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

**Results:**

These results are based on the analysis of 3 study groups: there were 50 cases suspected of having early neonatal sepsis. These were furtherly subdivided into 2 subgroups: probable and proven sepsis depending on the results of blood cultures. A positive blood culture was detected in 23 cases: these are the proven sepsis group. A negative blood culture was detected in 27 cases: these are the probable sepsis group. The third group was the control group, where a random sample was taken from 50 healthy neonates.




oFigure (1) Blood culture isolates among proven sepsis.

Table (1) Effect of sepsis on selected measurements

| Variables | | Controls | Probable sepsis (n= 27) | Proven sepsis (n= 23) | P Value |
|---|---|---|---|---|---|
| TLC | Mean | 9.664±3.6911 | 12.700±8.3963 | 14.070±7.0219 | 0.082 |
| | Median | 8.900 | 9.300 | 13.200 | |
| CRP | Mean | 3.00±1.429 | 11.42±11.497 | 67.83±64.830 | 0.0001 |
| | Median | 3.00 | 8.00 | 31.00 | |
| Cd64% | Mean | 63.787±25.5399 | 57.937±30.7826 | 67.217±30.2038 | 0.453 |
| | Median | 70.250 | 56.800 | 65.0 | |
| CD64 Mfi | Mean | 0.94358±1.8132 | 1.8901±1.16587 | 2.5322±1.62855 | 0.149 |
| | Median | 1.4950 | 1.4900 | 1.8000 | |
| Hla Dr% | Mean | 27.050±26.3744 | 16.667±17.1444 | 9.970±6.1905 | 0.001 |
| | Median | 13.500 | 10.800 | 8.400 | |
| Hla Dr Mfi | Mean | 2.607±0.7536 | 1.857±0.3998 | 1.666±0.5822 | 0.0001 |
| | Median | 2.475 | 1.800 | 1.520 | |
| Sepsis Index | Mean | 74.117±45.9005 | 105.582±73.2321 | 180.663±143.0085 | 0.0001 |
| | Median | 60.131 | 80.513 | 120.213 | |

Table (1) Effect of sepsis on TLC, CRP, CD64%, CD64 MFI, HLA DR%, HLA DR MFI and Sepsis Index in controls, probable and proven sepsis. Regarding CRP as shown in Table (1) there is significance of CRP with sepsis between control, probable and proven sepsis (P= 0.0001). Regarding CD64% on gated neutrophils, as shown in Table (1) there is no significance of CD64% with sepsis between control, probable and proven sepsis (P= 0.453). Regarding CD64 MFI, as shown in Table (1), there is no significance of CD64 MFI with sepsis between control, probable and proven sepsis (P= 0.149).

In HLA DR% gated on monocytes, the mean for the control group is 27.050± 26.3744, for the probable there is significance between HLA DR% and sepsis between control, probable and proven sepsis (0.001).

In HLA DR MFI, there is significance between HLA DR MFI and sepsis between control, probable and proven sepsis (0.0001).

## Introduction:

Neonatal sepsis, sepsis neonatorum and neonatal septicemia are clinical and laboratory findings suggestive of invasive infection during the first 28 days of life. Neonatal sepsis is defined as bacteremia associated with hemodynamic compromise and systemic signs of infection.(1) Before, the neonatal sepsis syndrome has been defined as bacteremia, but it may be caused by a variety of pathogens, including bacteria, viruses or fungi.(2) The first 28 days of life is defined as the neonatal period represent the most difficult time of a child's survival. According to WHO (2016), 2.6 million deaths, around 46% of all under- five deaths, took place in the neonatal period, which means 7000 newborn deaths per day. This mostly occurs in the first day and week, with around 1 million dying on the first day and an other one million in the following six days.

A study of 115 infants admitted to a neonatal intensive care unit (NICU) in Cairo University Hospital showed that 77% had sepsis, with hospital- acquired pathogens, and mortality rates exceeded 51% in a 3 month period.(3)

Neonatal sepsis is classified into early- onset neonatal sepsis (EONS) and late- onset neonatal sepsis (LONS). EONS is typically defined as sepsis occurring during the first 3 or 7 days after birth. Group B Streptococcus (GBS) sepsis usually occurs on day 3. LONS occurs as early as 4 or 8 days after delivery and as late as 28 days after delivery.(4) The bacterial origin of neonatal sepsis is related to the timing of the disease onset and has been variable.(5) The microorganisms most commonly causing early- onset infection include group B Streptococcus (GBS), Escherichia coli, coagulase- negative Staphylococcus, Haemophilus influenza.

Late- onset sepsis is caused by the environment. It is predisposed by vascular or urinary catheters, other indwelling lines, or contact from caregivers with bacterial colonization. Frequent organisms include E. coli (14- 23%), S. aureus (7%), coagulase negative staphylococci (CoNS; 5%), Haemophilus influenzae (4.5- 8%) and enterococci (4- 5%); While Gram-positive cocci are still dominant among term and near- term infants, Gram- negative rods can cause EOS among VLBW neonates in developed countries.(6) Hematological indices have poor specificity for diagnosing sepsis, and they can also have subjective errors, especially in estimating the band count and its derived immature/total neutrophil ratio. C-reactive protein (CRP) is a late marker of neonatal infection peaking ~24h after infection. It cannot truly determine sepsis, as it may be increased in other conditions also.(7)

The cluster of differentiation (cluster of designation) (often abbreviated as CD) is a protocol used for the identification and investigation of cell surface molecules present on white blood cells initially but found in almost any kind of cell of the body, providing targets for immunophenotyping of cells. CD64 is a type of integral membrane glycoprotein known as an Fc receptor that binds monomeric IgG- type antibodies with high affinity.(8) During bacterial infections, the FcRI (CD64) expression increases on neutrophils and triggers various important biological functions in cells, such as phagocytosis, activation of the oxidative burst, degranulation, and antibody dependent cytotoxicity.(9) CD64, a leukocyte surface antigen, is expressed at low concentration on surfaces of non- activated neutrophils. CD64 is a high- affinity Fc receptor that is upregulated during infection and sepsis.(10)

The human major histocompatibility complex, called the HLA region, is located on the short arm of chromosome 6. This region is known to code for about six proteins expressed on the cell surface and several serums complement factors. The HLA- controlled cell surface antigens are highly polymorphic both serologically and structurally. This polymorphism is essential for the function of these molecules which, evidence indicates, is to allow ceils of the immune system to discriminate self from non- self. The HLA region also controls the expression of the DR antigens. The DR antigens are found primarily on B lymphocytes and monocytes, but have also been detected on a variety of other somatic and tumor cells. HLA- DR is an MHC class II cell surface receptor, constituting a ligand for the T- cell receptor of T- helper cells. Monocytes strongly express HLA- DR and it is upregulated in response to signaling.(11)

HLA- DR seems to be more an early predictive prognostic marker for neonatal sepsis rather than a diagnostic marker, due to its rapid decrease issued by storage temperature and staining delay.(12)

When using the neonatal score of sepsis (SOS), the number of points for the laboratory markers and the number for clinical indicators are totaled for an individual newborn. The maximum possible score is 55, with 35 points for clinical indicators and 20 points for laboratory markers; total clinical score less than 10 indicates that the newborn does not have sepsis and total clinical score greater than 10 is considered sepsis.(13)

## Methodology

### Design:

This prospective study was conducted on 50 neonates who were admitted to the Neonatal Intensive Care Unit (NICU) at El Galaa Teaching Hospital and 50 healthy neonates as a (control group) in the period from June 2018 to June 2019. They were evaluated for neonatal sepsis with sepsis screen tests, blood culture and flow cytometry analysis.

Informed consent was taken from parents of our patients and controls.

1. Inclusion Criteria:
    a. Any suspected case of neonatal sepsis with maternal risk factors for sepsis e.g. prolonged labor, premature rupture of membrane (PROM) or prolonged PROM>18 hours, maternal intrapartum fever, urinary tract infection, chorioamnitis.
    b. Sepsis related clinical signs: temperature instability, apnea, need for supplemental oxygen, bradycardia, tachycardia, hypotension, hypoperfusion, feeding intolerance, abdominal distension.
2. Exclusion Criteria: Birth asphyxia, documented necrotizing enterocolitis (NEC), aspiration syndromes, laboratory finding suggestive of inborn error of metabolism, and congenital anomalies including congenital heart disease.

# A study of leukocyte surface antigen CD64, and monocyte surface antigen HLA DR as a marker of sepsis in preterm and full-term neonates

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**Summary**

**Background:** The diagnosis of sepsis is considered a real challenge as it requires a careful clinical suspicion, complete physical examination and tests. No single test can diagnose sepsis in neonates; however the combination of the above is the best method to diagnose.

**Aim:** This prospective study aimed to determine the sensitivity and specificity of CD64 (neutrophil surface antigen) and HLA DR (monocyte surface antigen) and to compare them to other parameters used to diagnose early neonatal sepsis. Also, to define the optimal cut off value for HLA DR MFI and SI using the receiver operating characteristics (ROC) curve so it may be used later on as a reference to compare with other studies.

**Methodology:** The study was conducted on 100 neonates collected from the NICUs of El Galaa Teaching Hospital and Cairo University Children Hospital. 50 infected cases and 50 healthy neonates (control group). For each case the following investigations were ordered: flow cytometry assessment of CD64 and HLA DR.

**Results:** We found that the percentage of neutrophils expressing CD64 was not higher in infected groups; however, HLA DR% is lower in infected group in comparison with the control group and SI are more significantly higher.

**Conclusion:** HLA DR MFI was proven to drop significantly in neonates with neonatal sepsis. CD64 doesn't show a significant role in diagnosing early neonatal sepsis. Other hematological tests such as CRP and TLC help in diagnosing and following sepsis.

**Keywords:** Neonatal sepsis, neutrophil CD64, flow cytometry, HLA DR. C- reactive protein, score of sepsis.

**استخدام CD64 وHLA- DR في تشخيص ومتابعة بكتريا الدم في الاطفال**

**الخلفية:** تشخيص الميكروب بالدم فى الاطفال حديثى الولادة يشكل مشكلة كبيرة لانه يحتاج شك اكلينيكي وفحص بدني كامل وفحوصات. لا يوجد اختبار واحد يمكن ان يشخص الميكروب ولكن مزيج من ما سبق هو افضل طريقة.

**الاهداف:** هذه الدراسة تهدف الي تحديد حساسية وخصوصية CD64 وHLA DR ومقارنتهم بالتحاليل الاخري المستخدمة للتشخيص المبكر للميكروب بالدم، وتحديد قيمة القطع المثالي لمؤشر الHLA DR MFI ونسبة الميكروب باستخدام منحني خصائص لتشغيل المستقبل بحيث يمكن استخدامه لاحقا كمرجع للمقارنة مع الدراسات الاخري.

**العينة:** أجريت هذه الدراسة في وحدة العناية المركزة لحديثي الولادة في مستشفى الجلاء التعليمي ومستشفى طب الأطفال بجامعة القاهرة. وقد أجريت الدراسة على ١٠٠ طفل حديثي الولادة، ٥٠ حالة مصابة و٥٠ حديثي الولادة الأصحاء (مجموعة المراقب) كل الاطفال المشاركين في البحث تم اخذ تاريخ مرضي دقيق لهم لكل حالة تم طلب التحاليل الاتية: صورة الدم كاملة ومستوي الغازات بالدم ومستوي السكر بالدم CRP واشعة للصدر وتقييم التدفق الخلوي لCD64 وHLA D.

**النتائج:** وجدنا أن نسبة العدلات التي تعبر عن CD64 لا تعبر عن الميكروب ولكن HLA DR أقل بكثير ونسبة الميكروب اعلي في مجموعة الميكروب، ومعامل اخري مثل عدد كرات الدم البيضاء وCRP تساعد في التشخيص لكن كل واحدة منفردة ليست كافية ولا قيمة لها. في هذه الدراسة اكثر العلامات المسؤولة عن الميكروب هو HLA DR MFI بمعدل دقة ٠,٨٥٦ بمؤشر تسمم= ٠,٧٩٨، لكن بالنسبة للCD64 MFI كان معدل الدقة ٠,٦٣٨.

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