



“STUDY OF THROMBOCYTOPENIA AMONG CASES OF NEONATAL SEPSIS”

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Abstract

Introduction: Thrombocytopenia is frequently associated with neonatal septicemia. In view of higher incidence of thrombocytopenia in neonatal sepsis, the serial platelet count should be done routinely in all cases of neonatal septicemia.

Aims and objectives: Study of thrombocytopenia among cases of Neonatal Sepsis

Methodology: 190 neonates with inclusion criteria taken for study from 21/03/18 to 31/04/19 in our NICU. Initial platelet count (day1) was recorded and was followed by on day 3, 6 , 9 (and as on when necessary) till the count reached the normal limit. Neonatal data like gender, gestational age, birth weight, occurrence of haemorrhage, use of platelet transfusion, blood investigations, length of hospital stay and neonatal mortality was recorded. Results of analysis and statistical data were recorded and presented in formulated tables.

Results: Thrombocytopenia was seen in 77.9% of septic neonates. Very Severe degree of thrombocytopenia was seen in 12.11% of septic neonates. The decreasing trend in the platelet count showed significant mortality (p value <0.05). In cases of mortality, 6 cases (13.95%) had very severe degree of thrombocytopenia.

Conclusion: In this study, we concluded that there was high incidence of thrombocytopenia in neonatal sepsis (77.9%). Klebsiella pneumoniae (38%) was the most common pathogen isolated in the blood culture. There was significant increase in the hospital stay in neonatal septicemia in culture positive cases (p value<0.05). On comparing serial platelet count it was found that, serial platelet was in a decreasing trend in neonates who had mortality. (p value<0.05), and in an increasing trend in the platelet count showed decreased mortality (p value<0.05). Hence, serial thrombocytopenia monitoring is necessary in neonatal sepsis.

Key Words: Neonatal sepsis; Thrombocytopenia; Platelet count; Serial platelet monitoring; Neonatal septicemia; Klebsiella pneumoniae; Mortality; Platelet transfusion; Blood culture; Neonatal intensive care unit.

Introduction

Neonatal thrombocytopenia is one of the most common haematologic problems encountered in neonatal intensive care unit. Though highly prevalent, much more information is needed to know about the mechanisms underlying thrombocytopenia and its relation with neonatal sepsis.[1] Normally thrombocytopenia occurs in 1-5% of Newborns, with severe thrombocytopenia in 0.1-

0.5%.[1] Thrombocytopenia (platelet count <1.5 Lakh cells/cumm) is one of the most common haematological problems in Neonatal Intensive Care Units (NICUs), with 20-35% of the NICU patients developing this problem before discharge from the hospital.

Neonatal sepsis is a common cause of neonatal morbidity and mortality with an annual incidence of 2-6/ 1000 live births in the developed countries of world. In the developing countries, the estimated incidence is 3-4 times higher and neonatal sepsis remains one of the most common reasons for admission in neonatal units[2]. Neonatal sepsis and meningitis continue to be major causes of morbidity and mortality in newborns, particularly in premature infants. Although improvements in neonatal intensive care have decreased the impact of early-onset sepsis (EOS) in term infants, preterm infants remain at high risk for both EOS and its sequelae. Very low birth weight (VLBW) infants are also at risk for late-onset sepsis[3]. Late onset neonatal sepsis (LONS) is a common complication in the Neonatal Intensive Care Unit (NICU) especially in premature infants, in whom the clinical presentation can be subtle and nonspecific. Thrombocytopenia is an important complication associated with neonatal sepsis.

Thrombocytopenia is frequently associated with neonatal septicemia. In view of higher incidence of thrombocytopenia in neonatal sepsis, the platelet count should be done routinely in all cases of neonatal septicemia. It is also important to consider variations and incidence of thrombocytopenia with neonatal septicaemia. It is important to find, if sepsis induced thrombocytopenia is more common among low birth weight (LBW) and preterm babies. Complications of Thrombocytopenia are frequently associated with mucosal bleeds (GIT) and purpura.

Materials and method

Study design : Analytical observational study.

Place of data : Department of paediatric, Neonatal Intensive Care Unit ,Rajarshee Chhatrapati Shahu Maharaj Government Medical College, Kolhapur

Duration of study: 21/3/2018 to 31/04/2019

Inclusion criteria:

1. Blood culture positive neonates. (OR)
2. Clinical septic neonates. (OR)
3. Septic screen positive neonates.

Exclusion criteria

1. Mother with history suggestive of Idiopathic Thrombocytopenic Purpura, Systemic Lupus Erythematosus and other autoimmune disorders.
2. Neonates with history suggestive of bleeding disorders in the family, trisomies, and other congenital disorder.

Algorithm

190 neonates with inclusion criteria was taken for study from 21/03/18 to 31/04/19 in our NICU

Initial platelet count (day1) was recorded followed by on day 3, 6, 9 (and as on when necessary) till the count reached normal limit and lowest platelet count during the septic episode were noted.(or)platelet count on the onset of clinical features of sepsis, followed by on day 3,6,9 were taken. Neonatal data like gender, gestational age, birth weight, occurrence of hemorrhage, use of platelet transfusion, blood investigations, length of hospital stay and neonatal mortality was recorded. Crammer's v correlation coefficient[v]-measure of correlation if both variables are categorical [neonatal sepsis with thrombocytopenia], 190 patients with inclusion criteria were studied from March 2018 to April 2019(13 months).

Results

Out of 190 neonates who were studied in our tertiary health care hospital, 81(42.63%) were females and 109(57.37%) were males. Males were more prone of infection as compared to females with percentage being 57.37% and 42.63% in males and females respectively. Preterm(66.84%) babies were at more risk for sepsis than term(33.16%) neonates. 121 cases had a positive growth on culture and 69 had no growth on cultures comprising 63.68 and 36.32 percent respectively. Out of 14 cases which had haemorrhage, 9 cases (64%) had pulmonary Hemorrhage, 3 cases(22%) had prick site Hemorrhage and 2 cases(14%) had intracranial Hemorrhage. Out of 190 cases studied, cultures in 46 cases (38%) grew Klebsiella sp, 31 cases (25.61%) grew Coagulase negative staphylococcus; 14 cases (11.57%) grew Actinobacter sp. Cultures for 8 cases (6.61%) came positive for Candida sp, 7 (5.78%) came positive for Pseudomonas sp and 6 (4.95%) are positive for E-coli. 3 (2.47%) cultures grew Enterobacter, 2 (1.6%) grew Enterococci sp, 2(1.6%) grew Non fermentor group of organisms, 2(1.6%) grew Enterococci. Out of 190 cases, 25 cases required platelet transfusion (13.15%)

Table 1: Platelet count of patients

Platelet count(cells/cumm)	No. of cases	Percentage(%)
<=20000	20	10.53
20000-50000	45	23.68
50000-100000	68	35.79
100000-150000	43	22.63
150000-250000	6	3.16
>250000	8	4.21
Total	190	100

Table 1 shows Out of the total number of cases i.e., 190, 23 babies were found to have a low platelet count of less than 20000 which comprised of 12.11%, while 45.79% cases comprising of 87 babies were found to have platelet counts between 20000-1L.

Table no. 2: Comparison of Gestational age and thrombocytopenia.

Gestational age (Weeks)	Thrombocytopenia						Total	P value
	0-2000	2000-50000	50000-100000	100000-150000	150000-250000	>250000		
	0	0	0	0	0	0		
<26	2	2	1	5	0	0	10	0.23

26-32	4	9	11	7	0	0	31	3
32-36	8	23	33	16	4	2	86	
36-40	6	11	23	15	2	5	62	
>40	0	0	0	0	0	1	1	
Total	20	45	68	43	6	8	190	

Table no. 2 shows that 20% of cases with very severe thrombocytopenia were of <26 weeks of gestation whereas 10% of the cases with very severe thrombocytopenia were >26 weeks gestation.

Table no. 3: Comprehensive details of mortality cases in my study are shown below in a tabular column.

Mortality in various parameters (n=43)		No. of cases	Percentage (%)
Gender	Female	16	37.21
	Male	27	62.79
Age	<3days	33	76.74
	>3days	10	23.26
Gestation	Preterm	30	69.77
	Term	13	30.23
Birth weight	<2.5kg	40	93.02
	>2.5kg	3	6.98
Platelet count	<1.5 lac	39	90.70
	> 1.5 lac	4	9.30
Culture	Positive	20	46.51

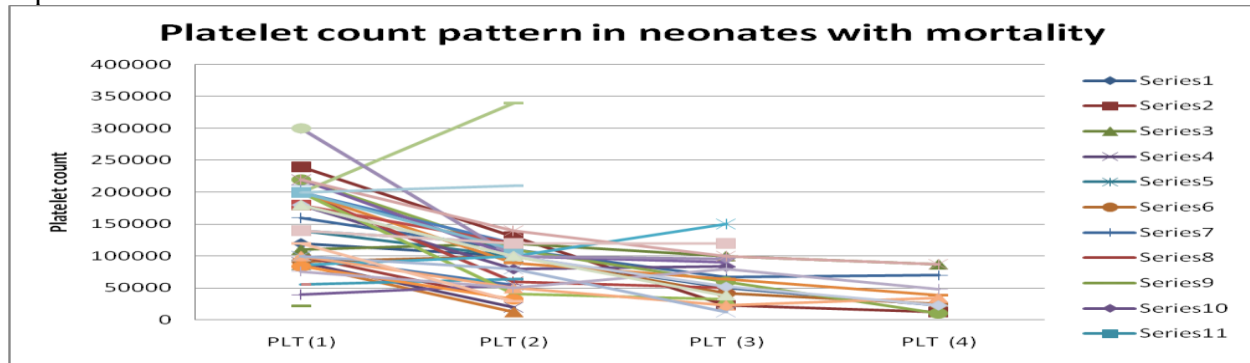
	Negative	23	
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Serial platelet count was recorded in all septic neonates and the chart was divided for statistical purpose and combined whenever needed for comparison. Serial platelet count in neonates with mortality or Klebsiella blood culture positive. Serial platelet count in neonates with discharge or non-Klebsiella blood culture positive. These tables below compare the serial platelet counts on admission, on day 3 of admission or less, on day 6 of admission or less, on day 9 of admission or less

Table no. 4: Comparing serial platelet counts(Average) in death and discharge neonates

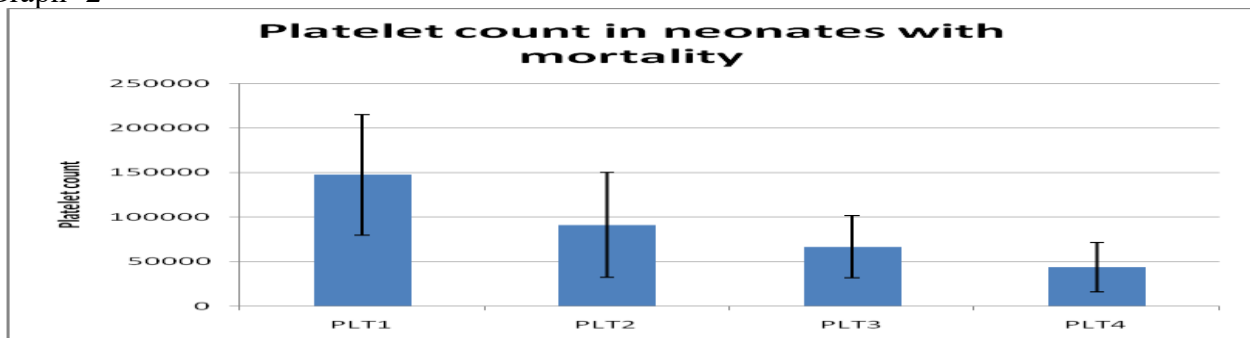
	Death	P value	Discharge	p value	P value
PLT (1)	147333.3±67405.04	nil	109353.7±69425.12	nil	<0.001
PLT (2)	91342.11±58883.89	<0.001	103285.7±65265.84	0.053	0.871
PLT (3)	66809.52±34757.18	<0.001	119363±53511.14	<0.001	<0.001
PLT (4)	43833.33±27712.27	0.002	134616.2±33439.77	<0.001	<0.001

Graph-1



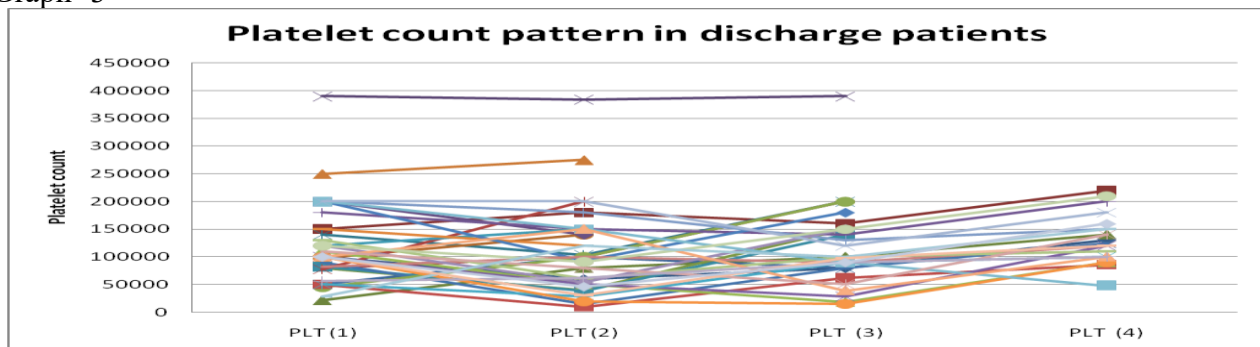
Graph 1. Decreasing Platelet count patterns noted in neonates with mortality

Graph -2



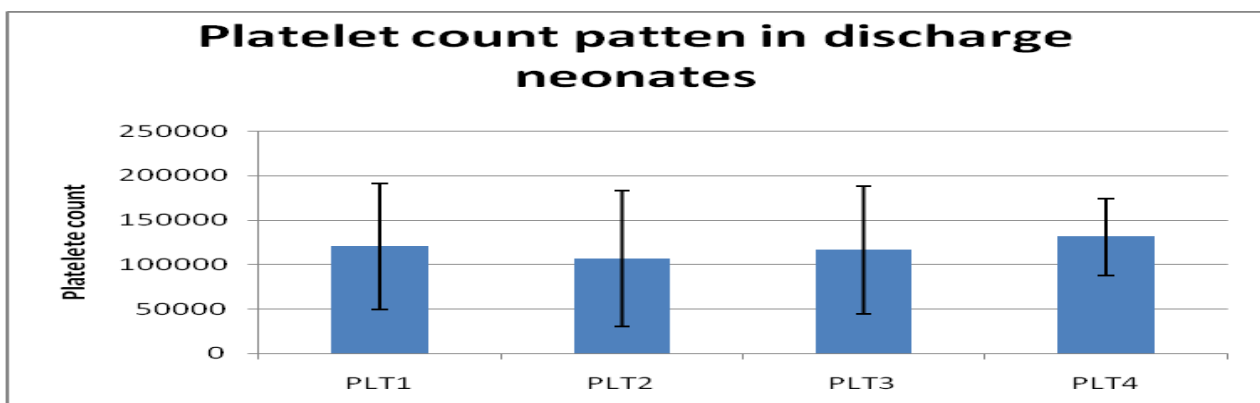
Graph 2. Average platelet count on sequential sample collected depicted in bar graph above in neonates with mortality

Graph -3



Graph 3 . Platelet count patterns noted in neonates who were discharged

Graph -4



Graph 4. Average platelet count on sequential sample collected depicted in bar graph above of neonates who were discharged

Discussion

Sepsis is the commonest cause of neonatal mortality in developing countries. One of the most difficult tasks faced by the neonatologist is to clinically differentiate between septicemic and non-septicemic cases. This is because several conditions like birth asphyxia, hypoglycemia, hypothermia, prematurity and intracranial hemorrhage have clinical features similar to septicemia.

The gold standard for diagnosis of neonatal sepsis is a positive blood culture which requires a minimum period of 48-72 hours and yields positive results in 25-70% of cases.[23,24,25,26]

The current study was undertaken to evaluate thrombocytopenia in neonatal septicemia and to look into various hematological parameters both individually and in combination as a part of sepsis screening.

Incidence of sepsis

Of the 190 neonates evaluated, 63.68% showed positive blood culture.

Age and sex incidence

The age of the neonates ranged from newborns to 28 days old. Of the 190 neonates in the study, 109(57.37%) were males and 81(42.63%) were females. In the sepsis proven group, 68 of the infants were males. Several other workers such as Philip and Hevitt⁸, Chandna et al.²⁰, Khatua et al.²⁴ and Gerdes et al.²⁷ have reported a similar finding. Male infants are 2-6 times more likely to develop neonatal sepsis than females.

Gestational age

There are 10 and 31 cases in the gestational age of <28 and 28-32 weeks respectively whereas 79 and 69 cases in 32-36 wks and 36-40 wks respectively. The lowest number of cases are in gestational age >40 weeks, the highest number of cases are in the 32-36 weeks comprising of 41.58%. Most of the infants with sepsis were preterm. In the preterm neonates, the inherent deficiencies are common in immune system, hence the risk of sepsis is increased as seen in several studies.[28,29,30]

Onset of symptoms

80% of the neonates in the study presented with early onset of sepsis. This is similar to the study conducted by Rodwell et al.²⁸ and Tallur et al.³¹. In the present study, 20% of the neonates had Late onset sepsis.

The most common pathogen isolated in the blood culture in the present study was *Klebsiella pneumoniae* followed by Coagulase Negative *Staphylococcus*. In the study conducted by Krishna et al.²¹ and Kumhar et al.²³, *Klebsiella* was the most common organism identified.

In contrast to the developed world where Group-B *Streptococcus*(GBS) continues to be the most common bacterial pathogen, studies from developing countries have identified Gram negative organisms as the more frequent infecting agent. Group B *Streptococcus* (GBS) and *Escherichia coli* account for about 60% of cases in North America and Europe. Hence even in the studies conducted by Rodwell et al.²⁸ and Philip and Hewitt³², GBS was the most common organism isolated. C Reactive protein levels were raised in 65.26% of neonates with sepsis. Comparisons of other studies are shown below

Platelet Count

Thrombocytopenia was seen in 65.26% of neonates in my study. In other studies like Mishra¹⁰⁵ (64%) , Ghosh S⁵ (70%) ,Bhandari V¹⁰⁶ (48%), Zaki and El Sayed¹⁰⁷ (41%), Makkar M⁸⁸ (81%). The incidence of thrombocytopenia in neonatal sepsis is higher.

Table no 8: Comparison of low platelet count with other studies.

Authors(Year)	Low platelet count
Mishra105	64%
Ghosh S5	70%
Bhandari V106	48%
Zaki and El Sayed107	41%
Makkar M88	81%
I Robert NA Murrey19	67.8%
Sartaj A Bhat14	66.2%
Von Lindern JJ52	67%
Present study	77.9%

Mortality studies comparison: In my study, 43 out of 190 neonates had mortality.

Mortality rates in various studies conducted since 1985 to 2019 which shows a significant amount of mortality seen in neonatal sepsis. My study has mortality of 22.6%. In other studies, the highest mortality is seen in Mishra JN108 which showed 61.7% mortality while lowest being 15.1% in Torkaman7 study.

Table no 9: Comparison of incidence of hemorrhage in neonates with other studies.

Name of Authors	Incidence of hemorrhage
Von Lindern JJ52	12%
Isabella12	6.3%
Present study	7.3%

Table no 9 shows comparison the incidence of hemorrhage in neonates with the studies of other authors. Lowest 6.3% is found in the study of Isabella12 while highest incidence of 12% is found in the study of Von Lindern JJ52. The incidence of hemorrhage in my study is 7.3%.

Table no 10: Comprehensive details of mortality cases in my study are shown below in a tabular column.

Mortality in various parameters (n=43)		No. of cases	Percentage
Gender	Female	16	37.21
	Male	27	62.79
Age	<3	33	76.74
	>3	10	23.26
Gestation	Preterm	30	69.77
	Term	13	30.23
Birth weight	<2.5	40	93.02

	>2.5	3	6.98
Platelet count	<1.5 lac	39	90.70
	> 1.5 lac	4	9.30
Culture	Positive	20	46.51
	Negative	23	53.49

Conclusion

In this study, we concluded that there was high incidence of thrombocytopenia in neonatal sepsis (77.9%) cases. *Klebsiella pneumoniae* (38%) was the most common pathogen isolated in the blood culture.

The advantage of studying thrombocytopenia and other hematological profile of neonates suspicious of having sepsis is that these tests can be done rapidly even in small hospitals earlier than blood cultures are obtained, allowing prompt treatment and at the earliest to neonates. Monitoring of platelet serial count also helps in predicting morbidity and mortality at the earliest before blood culture results, because sometimes absent to insignificant growth in cultures is found when antibiotics are given prior in the course of hospital stay. There was significant increase in the hospital stay in neonatal septicaemia in culture positive cases (p value<0.05).

On comparing serial platelet count (PLT count (1),(2),(3),(4) i.e, platelet count at admission and on 3rd , 6th , 9th , day respectively) in neonates who had mortality and those who were treated and discharged ,it was found that, serial platelet was in decreasing trend in neonates who had mortality. (p value<0.05), and increased trend in the platelet count showed decreased mortality(p value<0.05).Hence, serial thrombocytopenia monitoring is necessary in neonatal sepsis.

References

1. Ray RK, Panda S, Patnaik R, Sarangi G. Neonatal Thrombocytopenia.
2. Charoo BA, Iqbal J, Iqbal Q, Mushtaq S, Bhat AW, Nawaz I. Nosocomial sepsis-induced late onset thrombocytopenia in a neonatal tertiary care unit: a prospective study. Hematology/oncology and stem cell therapy. 2009 Apr 1;2(2):349-53.
3. Karne TK, Joshi DD, Zile U, Patil S. Study of Platelet Count and Platelet Indices in Neonatal Sepsis in Tertiary Care Institute. MVP Journal of Medical Science. 2017 May 22;4(1):55-60.
4. Ahmad P, Kaith R, Gattoo I, Najar BA, Hussain SQ. Thrombocytopenia as a predictor of neonatal sepsis in very low birth weight babies. Indian Journal of Neonatal Medicine and Research. 2015 Jul;3(3):7-13.
5. Ghosh S, Mittal M, Jaganathan G. Early diagnosis of neonatal sepsis using a haematological scoring system. Indian journal of medical sciences. 2001 Sep;55(9):495-500.
6. Khashu M, Osioviich H, Henry D, Al Khotani A, Solimano A, Speert DP. Persistent bacteraemia and severe thrombocytopenia caused by Coagulase-negative Staphylococcus in a neonatal intensive care unit. Paediatrics. 2006 Feb 1;117(2):340-8
7. Torkaman M, Afsharpaiman S, Hoseini MJ, Moradi M, Mazraati A, Amirsalari S, Kavehmanesh Z. Platelet count and neonatal sepsis: a high prevalence of Enterobacter spp. Singapore medical journal. 2009 May 1;50(5):482
8. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2003 Sep 1;88(5):F359-64.
9. Cloherty Manual of Neonatal Care (7th Edition) page 580
10. Ray RK, Panda S, Patnaik R, Sarangi G. Neonatal Thrombocytopenia.
11. Ree IM, Fustolo-Gunnink SF, Bekker V, Fijnvandraat KJ, Steggerda SJ, Lopriore E. Thrombocytopenia in neonatal sepsis: Incidence, severity and risk factors. PloS one. 2017 Oct 4;12(10):e0185581.

12. Sindhura YS, Reddy KR. A Study of Neonatal Thrombocytopenia in Neonatal Sepsis. *Journal of Contemporary Medical Research*. 2017;4(11):2250-2.
13. Goudar VR, Kabbini GM, Joshi SN, Chavan VP, Badiger SL. A study of bacterial sepsis and its relation to thrombocytopenia in neonates. *International Journal of Contemporary Paediatrics*. 2017 Apr 25;4(3):1032-6.
14. Bhat S, Naik S, Rafiq W, Tariq A. Incidence of thrombocytopenia and changes in various platelet parameters, in blood culture positive neonatal sepsis. *International Journal of Pediatrics*. 2015; 3(4.1):757-66.
15. Singh S, Agrawal A, Mohan U, Awasthi S. Prevalence of thrombocytopenia in neonates admitted in NICU with culture proven sepsis. *International Journal of Contemporary Pediatrics*. 2018 Apr 20; 5(3):743-8.
16. Arif SH, Ahmad I, Ali SM, Khan HM. Thrombocytopenia and bacterial sepsis in neonates. *Indian Journal of Hematology and Blood Transfusion*. 2012 Sep 1; 28(3):147-51.
17. The Harriet Lane Handbook, Twenty First Edition.
18. Nathan DG, Orkin Stuart H, A Thomas Look. Nathan and Oski's Hematology of infancy and childhood. 6th ed Philadelphia: Saunders; 2003
19. Dame C. Developmental biology of thrombopoietin in the human fetus and neonate. *Acta Paediatr Suppl* 2002;91 (438): 54-65
20. Chandna A, Nagaraj RM, Srinivas M, Shymala S. Rapid diagnostic tests in neonatal septicemia, *Indian J Pediatrics* 1988;55:947-953
21. Krishna BV, Nadgir SD, Tallur SS. Immunoglobulin M estimation and CRP detection in neonatal septicemia, *Indian JPM* 2000; 43(1):35-40
22. Ghosh S, Mittal M, Jaganathan G. Early Diagnosis of Neonatal Sepsis using a Hematological Scoring System 2001; *Ind. J Med Sci*, 55(9):495-500
23. Kumhar GD, Ramachandran VG, Gupta P. Bacteriological analysis of blood culture isolates from neonates in a Tertiary Care Hospital in India, *J Health Popul. Nutr* 2002;20(4):343-347
24. Khatua SP, Das AK, Chatterjee BP, Khatua S, Ghore B, Saha A. Neonatal Septicemia, *Indian J Pediatr* 1986;53:509-514
25. Monga K, Fernandez A, Deodhar L. Changing Bacteriological Patterns in Neonatal Septicemia, *Indian J Pediatr* 1986; 53:505-508
26. Joshi SG, Ghole VS, Niphadkar KB. Neonatal Gram Negative Bacteremia, *Indian J Pediatr* 2000;67(1):27-32
27. Gerdes JS, Polin R. Early Diagnosis and Treatment Of Neonatal Sepsis, *Indian J pediatr* 1998; 65:63-68
28. Poschl J.M, Ruef P, Schnouffer M, Pohl S. Group B Streptococcus Impairs Erythrocyte Deformability in neonates more than in adults, *Arch Dis Child Fetal Neonatal Ed*. 1996;74(3):187-190
29. Patrick CH, Lazarchick J. The effect of bacteremia on automated platelet measurements in neonates, *Am J Clin Pathol* 1990 Mar;93(3):39
30. Neonatal Bacteremia, Diagnosis and Management, *Br. Med J (Editorial)* 1997; 2:1385- 1386
31. Tallur SS, Kastur AV, Nadgir SD, Tallur SS. Clinicobacteriological study of neonatal septicemia in Hubli, *Indian J pediatr* 2000;67(3):169-174
32. Philip AGS and Hewitt JR. Early diagnosis of neonatal sepsis, *Pediatric* 1980;65(5):1036-41
33. Benitz WE, Han MY, Madan A, Ramachandra P. Serial Serum C-Reactive Protein levels in the Diagnosis of Neonatal Infection, *pediatrics* 1998;102(4):41-45
34. Deodhar S. C-Reactive Protein; The Best Laboratory Indicator Available for Monitoring Disease Activity, *Cleve clin J* 1989;56:126-130
35. Horns K.M. Neonatal Physiologic and Immunologic methods for Assessing Early – Onset Neonatal Sepsis, *J Perinat Neonat Nurs* 2000;13(4):50-66
36. Yentis SM, Soni N, Sheldon J. C-Reactive Protein as an Indicator of Resolution of Sepsis in the Intensive Care Med 1995;21:602-605

37. Larson L, Alexander JL. Disorder of primary hemostasis, chapter 36, clinical laboratory hematology, McKencie S, B, Pearson Education publishers, New Jersey 2004; 710-712
38. Greer JP, Foerster J, Lukens JN. Miscellaneous Causes Of Thrombocytopenia, Chapter 55, Wintrobe clinical Hematology 10th edition, Levine SP, Williams and Willkins, Volume 2 Philadelphia 2004; 1569-1570
39. Rodwell RL, Leslic AL, Tudehope DI. Early Diagnosis of Neonatal Sepsis using a Hematologic Scoring System, J. Pediatr: 1988; 112: 761-767
40. Guida JD, Kunig AM, Leef KH, Steven E, McKenzie, Paul D A. Platelet Count and Sepsis in very low birth weight neonates : Is there an organism specific response, Official Journal of American academy of Pediatrics 2003; 141: 1411-1415
41. Kumhar GD, Ramachandran VG, Gupta P. Bacteriological analysis of blood culture isolates from neonates in a Tertiary Care Hospital in India, J Health Popul. Nutr 2002; 20(4): 343-347
42. Aggarwal R, Sarkar N, Ashok K, Deorari, Paul VK. Sepsis in the newborn, Indian J pediatr 2001; 68: 1143-1147
43. Issacs D, Moxan ER. Neonatal Infections 1st Ed. Oxford, Butterworth Heireman Ltd, 1991: 149-166
44. Lukens JN. Blood formation in the embryo, fetus and newborn. wintrobes clinical Haematology Vol 1, 10 th Ed. Lee GR, Foerster J, Lukens F, Paraskevar JP, Green and G.M. Rodger, Chapter 2 Williams and Willkins, USA, 1999
45. I Roberts, NA Murray; Neonatal thrombocytopenia: Causes and management. Arch Dis Child Fetal Neonatal Ed 2003; 88: F359-F364
46. Manzoni P, Mostert M, Galletto P, Gastaldo L, Gallo E, Agriesti G, Farina D. Is thrombocytopenia suggestive of organism-specific response in neonatal sepsis?. Pediatrics International. 2009 Apr; 51(2): 206-10.
47. Corrigan Jr JJ. Thrombocytopenia: A laboratory sign of septicemia in infants and children. The Journal of pediatrics. 1974 Aug 1; 85(2): 219-21
48. Torkaman M, Afsharpaiman S, Hoseini MJ, Moradi M, Mazraati A, Amirsalari S, Kavehmanesh Z. Platelet count and neonatal sepsis: a high prevalence of Enterobacter spp. Singapore medical journal. 2009 May 1; 50(5): 482.
49. Brown RE, Rimsza LM, Pastos K, Young L, Saxonhouse MA, Bailey M, Lawrence RM, Sola-Visner MC. Effects of sepsis on neonatal thrombopoiesis. Pediatric research. 2008 Oct; 64(4): 399.
50. Jumah DS. Predictors of mortality outcome in neonatal sepsis. The Medical Journal of Basrah University. 2007; 25(1): 11-8
51. Bolat F, Kılıç SÇ, Oflaz MB, Gülhan E, Kaya A, Güven AS, Aygüneş U, İçağasıoğlu D, Gültekin A. The prevalence and outcomes of thrombocytopenia in a neonatal intensive care unit: a three-year report. Pediatric hematology and oncology. 2012 Oct 25; 29(8): 710-20.
52. Von Lindern JS, van den Bruele T, Lopriore E, Walther FJ. Thrombocytopenia in neonates and the risk of intraventricular hemorrhage: a retrospective cohort study. BMC pediatrics. 2011 Dec; 11(1): 16.
53. Bonifacio L, Petrova A, Nanjundaswamy S, Mehta R. Thrombocytopenia related neonatal outcome in preterms. The Indian Journal of Pediatrics. 2007 Mar 1; 74(3): 269-74.
54. Ververidis M, Kiely EM, Spitz L, Drake DP, Eaton S, Pierro A. The clinical significance of thrombocytopenia in neonates with necrotizing enterocolitis. Journal of pediatric surgery. 2001 May 1; 36(5): 799-803.
55. Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. The Indian Journal of Pediatrics. 2008 Mar 1; 75(3): 261-6.
56. Khatua SP, Das AK, Chatterjee BD, Khatua S, Ghose B, Saha A. Neonatal septicemia. The Indian Journal of Pediatrics. 1986 Jul 1; 53(4): 509-14.
57. Bhakoo ON. Neonatal bacterial infections at Chandigarh: A decade of experience. Indian journal of pediatrics. 1980 Sep 1; 47(5): 419-24.

58. Philip AG, Hewitt JR. Early diagnosis of neonatal sepsis. *Pediatrics*. 1980 May 1;65(5):1036-41.
59. Tallur SS, Kasturi AV, Nadgir SD, Krishna BV. Clinico-bacteriological study of neonatal septicemia in Hubli. *The Indian Journal of Pediatrics*. 2000 Mar 1;67(3):169-74.
60. Namdeo UK, Singh HP, Rajput VJ, Kushwaha JS. Hematological indices for early diagnosis of neonatal septicemia. *Indian pediatrics*. 1985 Apr;22(4):287-92.
61. Christensen RD, Rothstein G. Pitfalls in the interpretation of leukocyte counts of newborn infants. *American journal of clinical pathology*. 1979 Oct 1;72(4):608-11.
62. Chakravorty S, Murray N, Roberts I. Neonatal thrombocytopenia. *Early human development*. 2005 Jan 1;81(1):35-41.
63. Guclu E, Durmaz Y, Karabay O. Effect of severe sepsis on platelet count and their indices. *African Health Sciences*. 2013;13(2):333-8.
64. Ohlin A. Aspects on early diagnosis of neonatal sepsis (Doctoral dissertation, Örebro university).
65. Lee WS, Cho JY, Yoo ST, Lee CW, Choi DY, Kim JD, Oh YK. Platelet count and mean platelet volume in low birth weight infants ($\leq 2,000$ g) with sepsis. *Korean Journal of Pediatrics*. 2007;50(7):643-8.
66. Modanlou HD, Ortiz O, Gluck L. Thrombocytopenia in neonatal sepsis: Time relationship between clinical signs, detection of thrombocytopenia and positive blood culture. *Pediatric Research*. 1977 Apr;11(4):503.
67. Greer JP, Foerster J, Lukens JN. Miscellaneous Causes Of Thrombocytopenia, Chapter 55, *Wintrobe clinical Hematology 10th edition*, Levine SP, Williams and Willkins, Volume 2 Philadelphia 2004;1569-1570
68. Bain JB, Lewis SM, Bates I. Basic Hematological Techniques, Chapter 3, *Practical Hematology*, Dacie and Lewis, Bain J. B, Elsevier Publication, New Delhi 2008;51
69. Monga K, Fernandez A, Deodhar L. Changing Bacteriological Patterns in Neonatal Septicemia, *Indian J Pediatr* 1986; 53:505-508
70. Khatua SP, Das AK, Chatterjee BD, Khatua S, Ghose B, Saha A. Neonatal septicemia. *The Indian Journal of Pediatrics*. 1986 Jul 1;53(4):509-14.
71. Squire E, Favara B, Todd J. Diagnosis of neonatal bacterial infection: hematologic and pathologic findings in fatal and nonfatal cases. *Pediatrics*. 1979 Jul 1;64(1):60-4
72. Haider SA. Polymorphonuclear leucocyte count in diagnosis of infection in the newborn. *Archives of disease in childhood*. 1972 Jun 1;47(253):394-5.
73. Manroe BL, Rosenfeld CR, Weinberg AG, Browne R. The differential leukocyte count in the assessment and outcome of early-onset neonatal group B streptococcal disease. *The Journal of pediatrics*. 1977 Oct 1;91(4):632-7.
74. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. *Clinical microbiology reviews*. 2014 Jan 1;27(1):21-47.
75. Siegel JD, McCracken Jr GH. Sepsis neonatorum. *New England Journal of Medicine*. 1981 Mar 12;304(11):642-7.
76. Jain NK, Jain VM, Maheshwari S. Clinical profile of neonatal sepsis. *Kathmandu University medical journal (KUMJ)*. 2003;1(2):117-20.
77. Gupta I, Naskar P, Mitra G. Spectrum of bacterial infection and antimicrobial sensitivity pattern in neonatal septicemia in a peripheral tertiary care hospital in West Bengal. *International Journal of Contemporary Medical Research*. 2016;3:2669-71.
78. . Shah BA, Padbury JF. Neonatal sepsis: an old problem with new insights. *Virulence*. 2014 Jan 1;5(1):170-8.
79. . Haque KN. Neonatal sepsis in the very low birth weight preterm infants: Part 2: Review of definition, diagnosis and management. *Journal of Medical Sciences*. 2010 Jan 1;3(1):11-27.
80. Xanthou M. Leucocyte blood picture in healthy full-term and premature babies during neonatal period. *Archives of Disease in Childhood*. 1970 Apr 1;45(240):242-9.

81. Hornik CP, Benjamin DK, Becker KC, Benjamin Jr DK, Li J, Clark RH, Cohen-Wolkowicz M, Smith PB. Use of the complete blood cell count in early-onset neonatal sepsis. *The Pediatric infectious disease journal*. 2012 Aug;31(8):799.
82. Hornik CP, Benjamin DK, Becker KC, Benjamin Jr DK, Li J, Clark RH, Cohen-Wolkowicz M, Smith PB. Use of the complete blood cell count in late-onset neonatal sepsis. *The Pediatric infectious disease journal*. 2012 Aug;31(8):803.
83. Jumah DS. Predictors of mortality outcome in neonatal sepsis. *The Medical Journal of Basrah University*. 2007;25(1):11-8.
84. Guclu E, Durmaz Y, Karabay O. Effect of severe sepsis on platelet count and their indices. *African Health Sciences*. 2013;13(2):333-8.
85. Wadile RG, Bhate VM. Study of clinical spectrum and risk factors of neonatal candidemia. *Indian Journal of Pathology and Microbiology*. 2015 Oct 1;58(4):472.
86. Kumar V, Singhi S. Predictors of serious bacterial infection in infants upto 8 weeks of age. *Indian pediatrics*. 1994;31:171-.
87. Newman TB, Draper D, Puopolo KM, Wi S, Escobar GJ. Combining immature and total neutrophil counts to predict early onset sepsis in term and late preterm newborns: use of the I/T2. *The Pediatric infectious disease journal*. 2014 Aug;33(8):798.
88. Makkar M, Gupta C, Pathak R, Garg S, Mahajan NC. Performance evaluation of hematologic scoring system in early diagnosis of neonatal sepsis. *Journal of clinical neonatology*. 2013 Jan;2(1):25.
89. Mathur NB, Khalil A, Sarkar R, Puri RK. Mortality in neonatal septicemia with involvement of mother in management. *Indian pediatrics*. 1991 Nov;28(11):1259-63.
90. Castle V, Andrew M, Kelton J, Giron D, Johnston M, Carter C. Frequency and mechanism of neonatal thrombocytopenia. *The Journal of pediatrics*. 1986 May 1;108(5):749-55.
91. Craft A, Finer N. Nosocomial coagulase negative staphylococcal (CoNS) catheter-related sepsis in preterm infants: definition, diagnosis, prophylaxis, and prevention. *Journal of Perinatology*. 2001 Jul 19;21(3):186.
92. Behrman RE, Christensen RD, Bradley PP, Rothstein G. The leukocyte left shift in clinical and experimental neonatal sepsis. *The Journal of pediatrics*. 1981 Jan 1;98(1):101-5.
93. Bolat F, Kılıç SÇ, Oflaz MB, Gülhan E, Kaya A, Güven AS, Aygüneş U, İçağasıoğlu D, Gültekin A. The prevalence and outcomes of thrombocytopenia in a neonatal intensive care unit: a three-year report. *Pediatric hematology and oncology*. 2012 Oct 25;29(8):710-20.
94. Russell AR. Neonatal sepsis. *Paediatrics and child health*. 2011 Jun 1;21(6):265-9.
95. Satar M, Özlü F. Neonatal sepsis: a continuing disease burden. *The Turkish journal of pediatrics*. 2012 Sep 1;54(5):449.
96. Dewitte A, Lepreux S, Villeneuve J, Rigothier C, Combe C, Ouattara A, Ripoche J. Blood platelets and sepsis pathophysiology: A new therapeutic prospect in critical ill patients?. *Annals of intensive care*. 2017 Dec;7(1):115.
97. Christensen RD. Origins of the discipline „Neonatal Haematology“ 1925-75, *Br J Haemat* 2001;113:853-860
98. Benirschke K. Routes and types of infection in fetus and newborn, *Am J Dis Childhood* 1960;99:714-21
99. Ablin AR, Kushner JH, Murphy A, Zippin C. Platelet enumeration in the neonatal period, *pediatrics* 1961;82:822-23
100. Zipursky A, Palko J, Milner R, Akenzua GI. The hematology of bacterial infections in premature infants, *pediatrics* 1976;57(6):839-53
101. Philip AGS and Hewitt JR. Early diagnosis of neonatal sepsis, *Pediatric* 1980;65(5):1036-41
102. Freedman RM, Ingram DL, Gross I, Richard A, Ehrenkranz, Warshaw JB et al. A Half century of neonatal sepsis at yale 1928 to 1978, *Am J Dis Child* 1981;(135):140-144
103. Report of the National Neonatal Perinatal Database (National Neonatology Forum), 2002-2003.
104. Ohlin A. Aspects on early diagnosis of neonatal sepsis, *Orebro University*. 2010:9-77.

- 105.Mishra PK. Simple hematological tests for diagnosis of neonatal sepsis. *Indian Pediatrics*. 1989;26:156-61.
- 106.Bhandari V, Wang C, Rinder C, Rinder H. hematologic profile of sepsis in neonates: neutrophil CD64 as a doagnostic marker. *Pediatrics*. 2008; 121:129-34.
- 107.Zaki and El Sayed. Evaluation of Microbiological and Hematologic parameters and E-Selectin as early predictors for outcome of neonatal sepsis. *Arch Pathol Lab Med*. 2009;133:1291-6.
- 108.Mishra JN. Study of neonatal septicemia. *India Pediatrics*. 1985; 12:281.
- 109.Duha Sabeeh Jumah, Mea'd Kadham Hassan. Predictors of mortality outcome in neonatal sepsis. *The medical journal of Basrah University*. 2007;25(1): 11-8.
- 110.Anand NK, Gupta AK, Mohan M. Coagulase negative staphylococcal septicemia in newborns. *Indian Pediatrics*. 1991; 28:1241-1248.
- 111.Mehrotra N, Kumar A, Chansoria M, Kaul KJC. Neonatal sepsis: correlation of maternal and neonatal factors to positive bacterial cultures. *Ind Pediatrics*. 1985; 22:275-80.
- 112.Namdeo VK. Hematological indices for early diagnosis of neonatal septicemia. *Indian Pediatrics*. 1985; 22:287.
- 113.Afsharpaiman S, Torkaman M, Saburi A. Trends in incidence of neonatal sepsis and antibiotics susceptibility of causative agents in two Neonatal Intensive Care units in Tehran IR. *J Clin Neonatal*. 2012 july;1(3): 124-130.
- 114.Placzek MM, Whitelaw A. Early and late neonatal septicemia. *Arch Dis Child*. 1983;58: 728-31.
- 115.Maucha V,Rusia U,Sikka M,Faridi MMA,Madan N.Utility of Hematological parameters and C-Reactive protein in the detection of Neonatal Sepsis, *J Pediatr and Child Health* 2002;38:459