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Can we use NNT (neonatal thrombocytopenia) as a screening tool in at risk neonates for diagnosing neonatal septicaemia

Dr.K.V.Subba Rao[1,] Associate Professor of Pediatrics, Niloufer Hospital, Osmania Medical College, Hyderabad. Dr.B.Koteshwar[2] Assistant Professor of Pediatrics, Niloufer Hospital, Osmania Medical College, Hyderabad.Dr.Ch.Sudhakar[3] Postgraduate of Pediatrics, Niloufer Hospital, Osmania Medical College, Hyderabad,.

Abstract:
Objective: *Can we use NNT (neonatal thrombocytopenia) as a screening tool in at risk neonates to screen NNS (neonatal sepsis). It is an easy and cost effective method.*
Design: *Prospective observational cross sectional descriptive study.*
Setting*: 'At risk neonates' are taken for the study for a period of 1 year (from Jan 2011 to Dec 2011) in level III NICU of Institute of Child and Women Health, Niloufer Hospital, Osmania Medical College, Hyderabad.*
Participants: *Over a period of 12 months, 215 neonates under the age of 28 days are admitted in NICU, in that111 'at risk term neonates' were detected. 6 neonates were excluded because they are associated with syndromes.*
Methods: *For all' at risk neonates' septic screening was done, wherever necessary blood culture was sent and compared those with septic screen positive and with septic screen negative. For septic screen TLC <5000cumm, CRP >6mg/l, ANC<1800/cumm, micro ESR >15mm, positive blood culture are taken and ≥2 risk factors were taken as high risk for sepsis and ≥2 septic screen positive neonates are considered as having sepsis, remaining as "at risk neonates without sepsis." Positive blood culture is taken as confirmed sepsis and included into the study, but it is not always imperative that have to be positive, because only 50- 80 % will be positive.*
Results: *This study is comprised of 105 neonates (58 neonates are male and 47 neonates are female) out of which 92 neonates had clinical diagnosis of septicemia. The M:F ratio is 1.23:1. In EOS group, out of 45, 35(77.80%) are having thrombocypenia and in LOS group out of 47,41(87.2%) are having thrombocytopenia. In this study sensitivity is 82.60% and specificity is 84.615%. Positive predictive value is 93.827% and negative predictive value is 45.83% and percentage of false negatives are 17.39 and percentage of false positive 15.34. The p value is 0.2942 suggests that sepsis not affected by sex. Of the 105 'at risk neonates' 31 are home deliveries. In 45 cases of EOS 13 are culture positive. In 47 cases of LOS 13 are culture positive.*
Conclusion: *Thrombocytopenia can be a useful tool for diagnosing neonatal septicaemia.*
Key words: *Neonatal septicaemia, neonatal thrombocytopenia, early onset sepsis (EOS), late onset sepsis (LOS), screening tool*

I. Introduction

Neonatal thrombocytopenia[1] (NNT) is one of the most common hematological problem encountered in NICU admitted cases particularly in septic babies and premature babies. Platelet count and mean platelet volume in the newborn are similar to those in adults and in children and ranges from 1,50,000/cumm up to 4,50,000/cumm and 7.5fl respectively. Premature infants on an average have slightly lower platelet count than full term infants but practically within normal range. There are 5 million neonatal deaths/year, of which sepsis accounts for 30-50% and in that 98% occurs in Developing countries.[1,2] Neonatal mortality rate (NMR)[3] was 31.6(28.9 - 34.5) /1000 in year 2011[3] . The Millennium goal for 2015 is to bring down to <20/1000 live births. A quarter of all neonates[4] in NICU develop NNT, 20% of them will have severe NNT. In India the incidence of

Neonatal sepsis (NNS) according to the data from National Neonatal Database (NNPD, 2002 – 03) is 30 per 1000 live births, and found sepis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths[5]. NNS is the most common cause of neonatal thrombocytopenia (NNT). Platelet life span is 10-14days. The platelets play multiple hemostatic roles. The platelet surface possesses receptors for adhesive proteins, including von Willebrand factor (vWF) and fibrinogen, as well as receptors to trigger platelet aggregation, such as thrombin, collagen and adenosine diphosphate (ADP). After injury to the blood vessel wall, sub endothelial collagen binds vWF. vWF undergoes a conformational change that includes binding of the platelet glycoprotein Ib (GPIb) complex with the VWF receptor. Platelets then undergo activation. During the process of activation, the platelets generate thromboxane A_2 from arachidonic acid via the enzyme cyclo-oxygenase. After activation, they release agonists, such as ADP, adenosine triphosphate (ATP), Ca^{2+}, serotonin, and coagulation factors, into the surrounding milieu. Circulating fibrinogen binds to its receptor on the activated platelets, the glycoprotein IIb-IIIa (GPIIb-IIIa) complex, linking platelets together. This series of events forms a

haemostatic plug at the site of vascular injury. The serotonin and histamine that are liberated during activation increase local vasoconstriction. In addition to acting in concert with the vessel wall to form the platelet plug, the platelet provides the catalytic surface on which coagulation factors assemble and eventually generate thrombin through a sequential series of enzymatic cleavages. The platelet contractile proteins and cytoskeleton mediate clot retraction.

The major mechanism responsible for thrombocytopenia in infected neonates is accelerated platelet destruction (immune mediated platelet destruction), decreased production and a minority of infected infants has Disseminated Intravascular Coagulation (DIC).

Thrombocytopenia may be found in up to 90% of newborns with NEC, with platelet counts of less than 50000/cumm in about half of the cases. In absence of DIC, clinical bleeding abnormalities are rare. Sepis is the commonest cause of neonatal mortality; it is responsible for about 30-50% of the total neonatal deaths in developing countries[2]. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes. Sepsis related mortality is largely preventable with rational antimicrobial therapy and aggressive supportive care.

II. Materials And Methods:

A prospective observational cross sectional descriptive study was designed and neonatal thrombocytopenia was taken as screening tool in 'at risk neonates[6]'. All 'at risk neonates' who were admitted in level III NICU were taken into the study. Neonates with sepsis who were 72hrsof age or less were taken as Early Onset neonatal Sepsis (EOS)[7] . Neonates with sepsis who were > 72hrsof age and less than 28 days was taken as Late Onset neonatal Sepsis (LOS)[8] . Approval was taken from the ethics committee of Osmania medical college, Hyderabad. Informed consent was taken from parents/guardian. A detailed history and physical examination was done. Sensitivity(Sn), specificity(Sp), PPV (positive predictive value) and NNP (negative predictive value) of neonatal thrombocypenia in 'at risk neonates' for NNS are calculated. Statistical analysis is performed applying MICROSOFT EXCEL 2007. EPI. INFO.3.5.3.

Inclusion criteria:

1. 'At risk neonates'
2. All culture positive sepsis cases who are screening negative

Exclusion criteria: Mothers with PIH, preeclampsia CCHD[9], ITP/SLE/medications[10,11,12] causing thrombocytopenia, family history of bleeding disorder, dysmorphic neonates, neonates who presented with severe bleeding, chromosomal disorders and those who required exchange transfusion.

This is a hospital based prospective observational study conducted over a period of 12 months, from April 2011 to March 2012 at Institute of Women and Child Health, Niloufer Hospital, Osmania Medical College, Hyderabad which is a teaching institute with a tertiary level NICU (level III) care.

Over 12 months, 215 neonates under the age of 28 days are admitted and 111 'at risk neonates' were studied and 6 neonates are excluded (2 Downs syndrome, 1 TAR syndrome, 1 with maternal SLE,2 cases of Congenital Heart Disease),105 neonates are included in this study.

Out of 105neonates, 92 of them were diagnosed as clinical diagnosis of sepsis. 'At risk neonates' the following criteria was followed.

A. In history

1. Foul smelling liquor
2. Febrile illness in the mother within 2 weeks prior to delivery
3. Meconium stained liquor amnii
4. Prolonged rupture of membranes > 24hrs
5. More than three vaginal examinations during the labour.
6. Prolonged and difficulty delivery with instrumentation.
7. Perinatal asphyxia (APGAR<4 at 1 min) or difficult resuscitation.

B. 12 symptoms or signs in neonate

1. Refusal of feeds
2. convulsions
3. lethargy / poor cry
4. respiratory rate of 60 breaths / minute or more
5. grunting
6. severe chest indrawing
7. hypothermia (temperature less than 35.5^0 C)
8. fever (temperature more than 37.5^0 C)
9. prolonged Capillary Refill Time)
10. Cyanosis

Presence of any one sign had high sensitivity (87%) and specificity (74%) (WHO and AIIMS: vol. 23.No.1 Jan – Mar – 2009) www.indianjournals.com
Thus presence of >2 signs / symptoms are taken as clinical sepsis and subjected for septic screen (GOLD STANDARD)
C. neonates with other factors to be subjected for GOLD STANDARD are
1. Factors that predisposed to an increased risk of nosocomial sepsis (invasive procedures, parentral fluid therapy, ventilation and use of stock solutions)
2. Factors that may increase risk of community – acquired late onset sepsis – poor hygiene, poor card care, bottle feeding
3. Hypotonia / absent neonatal reflexes, brady / tachycardia
My GOLD STANDARD is septic screening +ve with ± Blood culture positive
Septic screen[13,14]
1. CBP[15]
a.TLC[16] (<5000/cumm or >15000/cumm)
b.ANC[17,18] (<1800/cumm)
c. Immature to Total Neutrophil (I/T) ratio[19]: > 0.2 (immature neutrophils, band forms, metamyelocytes, myelocytes)/ mature + immature neurtophils
1. CRP[20]: >6 mg/dl (our microbiology reference)
2. Micro ESR[21,22]: > age in DOL +3 mm or > 15 mm/1st hour
3. Interleukin 6 (IL6), Procalcitonin not included due to practical problems
4. Blood culture
≥2 positive screening parameters (TLC, ANC, I/T ratio, CRP, μ-ESR) taken as septic screen positive (Sensitivity 93%, Positive Predictive value 39%, >2 parameters Negative the Negative Predictive Value 99%) and that neonate considered as septic.

Those with positive blood culture and / or positive septic screening were included in my study as "Septic Neonates" and remaining as "at risk neonates without sepsis"
Positive blood culture was taken as confirmed sepsis and included into study, but it was not always imperative that have to be positive, because only 50- 80 % will be positive because small inoculum, transient bacteraemia and pre exposure prior to antibiotics.

Blood was collected with all aseptic precautions in BD Vacutainer EDTA tube and in blood culture bottle and transported to respective laboratory for platelet count and blood culture quickly. Platelet count is performed by hemocytometer as a part of complete blood count and blood culture was done after inoculation of blood into blood culture bottle containing BHI with 0.025% sodium polyanethol sulfonate, it was incubated at 37°C for 7 days, subculture was done on blood agar and MacConkey's agar media after 24 h and 7 days of incubation. Blood culture was reported sterile if no growth was seen on subculture after 7 days of incubation. If any neonate was found to have incidental thrombocytopenia,they were also included and subjected to further investigation. If strong suspicion of sepsis was there & septic screen was negative, we repeated the screen after 24 hours. Platelet count done by hemocytometer and meticulous precautions were taken to prevent observational and inter observer variation. Spurious thrombocytopenia may occur in cell auto – analyzers, hence platelet count was done by manual method.

The following investigations were done in neonates, PCV (polycythemia), Ultra sound abdomen (renal vein thrombosis), CXR, 2DEcho (Congenital Heart Disease), Blood grouping and typing of mother and child (Rh – HDN) etc, as clinically demanded.
Cases were followed for only neonatal period or till discharged / demise
Observations: This study comprised of 105 neonates (58 neonates are male and 47 neonates are female) out of which 92 neonates had clinical diagnosis of septicemia. The M: F ratio 1.23:1. In early onset of sepsis group 28(62.22%) were male and 17(37.78%) were female neonates. In late onset of sepsis group 22(46.80%) were male and 25(53.20%) were female neonates. In non septic group 8 (61.53%) were male and 5 (38.47%) were female neonates.

In EOS group, out of 45, 35(77.80%) are having thrombocypenia and in LOS group out of 47, 41 (87.2%) are having thrombocytopenia

Table.1.

Platelet count	EOS	LOS	NOS	TOTAL
<0.5lakhs / mm3	12	14	2	28(34.56%)
0.5 – 1 lakh / mm3	7	10	1	18(22.22%)
1 lakh - < 1.5 lakhs mm3	16	17	2	35(43.20%)
TOTAL	35	41	5	81

These results were statistically analyzed by using MICROSOFT EXCEL 2007.EPI.INFO.3.5.3. The values obtained are as follows–

In our study sensitivity is 82.60% and specificity is 61.538%. Positive predictive value is 93.827% and negative predictive value is 33.33% and percentage of false negative are 17.39% and percentage of false positive 38.461%.

Sepsis burden: Out of 105'at risk neonates' 92 (87.61%) neonates were septic screen positive.

Age distribution: Based on the age of the baby, 'at risk neonates' were further categorized into early onset sepsis(EOS) for neonates who were 72 hour of life or less and late onset neonatal sepsis (LOS) for those who were > 72 hours of life but less than 28 days. There were 51 neonates in EOS group and 54 were in LOS group.

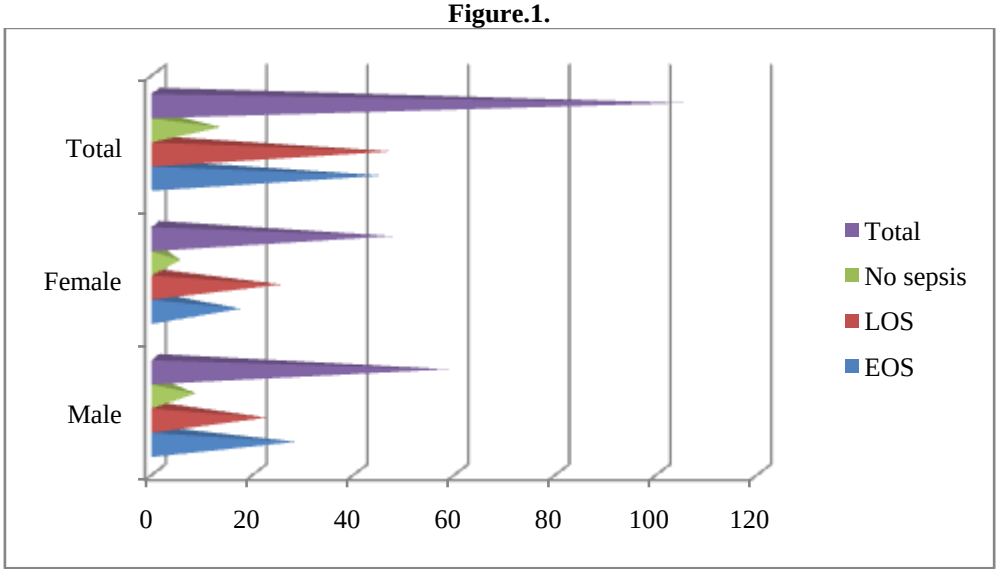
Sex Distribution: Of 105 'at risk neonates' 58 (55.24%) were male babies and 47 (44.76%) were female babies. In EOS group 28 (62.22%) were male and 17(37.77%) were female neonates. In LOS group 22(46.80%) were male and 25(53.19%) were female neonates. In without sepsis group 8were male and 5 were female neonates.

Table.2.

	EOS	LOS	Total
Male	28	22	50
Female	17	25	42
Total	45	47	92

P value is 0.2942.It suggests that sepsis is not affected by the sex of the neonate. Male were slightly more affected than female neonates.

Figure.1.



Birth weight distribution:

Based on the birth weight, the distribution of these babies into EOS and Los groups were as follows

Table.3.

Birth weight	EOS			LOS		
	Male	Female	Total	Male	Female	Total
<2.5kgs	17	11	28	12	10	22
>2.5kgs	11	6	17	10	15	25

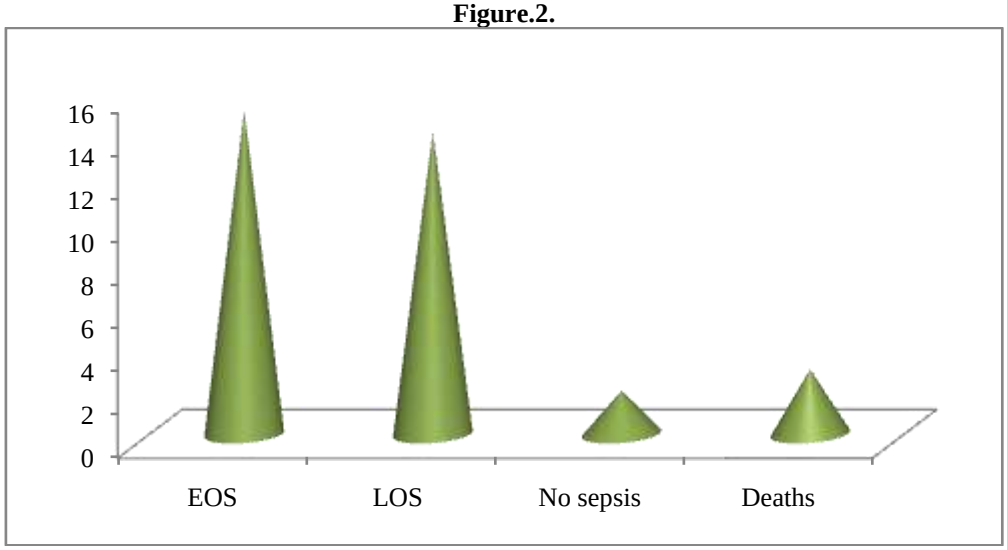
P value is 0.1380. The P value is insignificant in this study and it suggests that birth weight did not affect platelet count to the extent of significant levels to influence our study results.

Place of Delivery: Of the studied 105 'at risk neonates' 74 neonates were delivered in hospitals and remaining (31) were delivered at home. Out of 31 deliveries 2 babies were in no sepsis group 15 were in EOS group and 14 were in LOS group.

Table.4.

Home deliveries	31
EOS	15
LOS	14
NOS	02
Deaths	03

Figure.2.



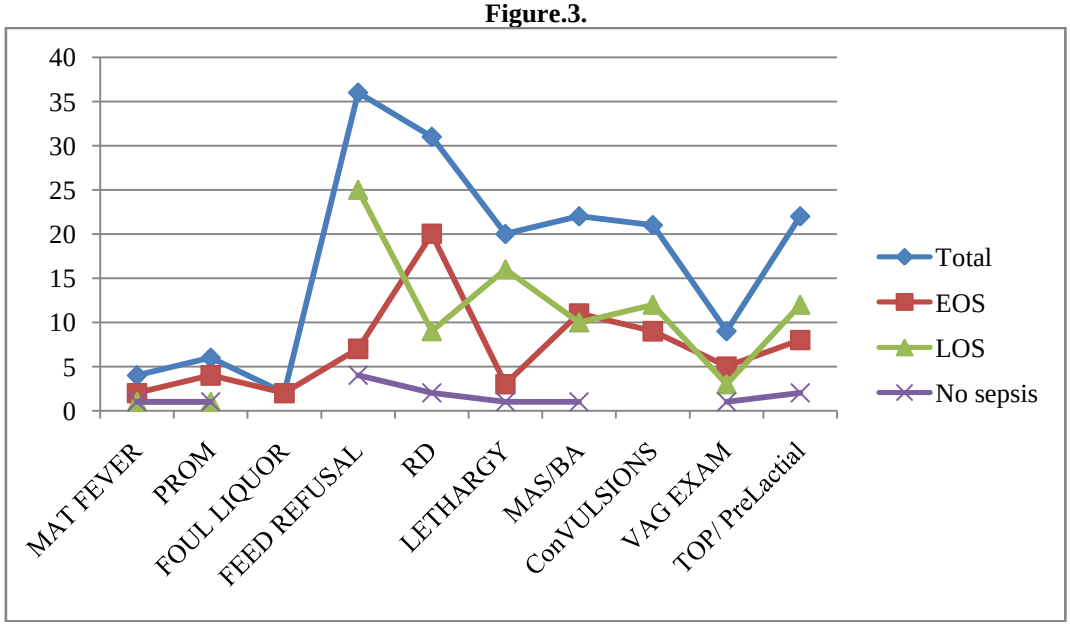
Clinical Presentation:

Table.5.

Clinical Presentation	EOS	LOS	No Sepsis	TOTAL
Maternal fever	2	1	1	4
Prolonged Rupture Of Membranes (PROM)	4	1	1	6
Foul smelling liquor	2	0	0	2
Refusal feeds	7	25	4	36
Respiratory Distress	20	9	2	31
Lethargy	3	16	1	20
MAS/ BA	11	10	1	22
Convulsions	9	12	0	21
Repeated Vaginal Examinations (>3)	5	3	1	9
Top / pre-lacteal feeds	8	12	2	22

Most common presentation in EOS group was respiratory distress and in LOS group was refusal of feeds and over all common presentation was refusal of feeds.

Figure.3.



Blood culture is positive in 26 (24.76%) cases out of 105 at risk neonates.

Table.6.

Group	Blood culture +ve	Blood Culture –ve	Total
EOS	13	32	45
LOS	13	34	47
No sepsis	0	13	13
Total	26	79	105

The P value is 0.8959.It suggests that blood culture and sensitivity was not affected by time of onset of sepsis. The following organisms were isolated in 26 cases on blood culture. The organisms were sensitive to Vancomycin and Cefoperazone.

Distribution of culture positive cases

Table.7.

Sl.No	Microorganism	No of cases
1.	Klebsiella	13(50%)
2.	Coagulase negative staphylococci	8 (30.76%)
3.	Enterococci	5 (19.24%)

Out Come of the Patients:

Table.8.

	Deaths			Discharged
	Male	Female	Deaths	
EOS	5	3	8	37
LOS	4	3	7	40
TOTAL	9	6	15	77

Five cases (5.8%) of the study group developed DIC. The bacteria, which were isolated in these cases, were Klebsiella. Specific antibiotic after culture sensitivity along with FFP and platelet transfusion were given in these cases. Out of these five cases, three cases (3.5%) were recovered and platelet counts were increased and reached to normal limit in 14–16 days. Two cases (2.3%) died of the disease. The cause of death was DIC and patients developed petechiae and bleeding from various sites including internal bleeding. The platelet count reduced to 5,000/µl. Broad spectrum antibiotic was given in those cases where blood cultures were negative and specific antibiotic was given after sensitivity, in those cases where blood cultures were positive. Patients responded to treatment, platelet counts increased and reached to normal within 10–14 days with improvement of clinical condition of neonates. All 83 neonates were discharged from the hospital after recovery.

III. Discussion:

Identification of infection in an infected infant without blood culture is a problem and culture positive sepsis in sophisticated NICUs ranges from 26% to 68%. So for this reason we have taken thrombocytopenia as a parameter to diagnose the septicaemia as early as possible with simple cost effective tool in septic screen. Still about 1/3rd deliveries are conducted at homes without proper hygiene where neonate is exposed to septic conditions. Here in our tertiary care hospital we are receiving almost 42.79% of all NICU admissions as burden of sepsis. Khalada Binte Khair et al[23] studied the 'Role of Hemotologic Scoring System in Early Diagnosis of septicaemia; they found that platelet count <1,00,000/cumm had sensitivity of 60% and specificity of 82 %,PPV 31% and NPV 94%. In our study it was found that NNT (1,50,000/cumm) can be used to screen neonate with sepsis with Sensitivity of 82.6%, and Specificity of 61.53% , Positive predictive value of 93.827% especially in 'at risk neonates' which is cost effective and available in almost all hospitals, particularly useful in developing countries like India. It requires further large scale studies and meta analysis to validate NNT as a screening tool in neonatal sepsis. The incidence of septicaemia is higher in male babies than female babies, which has been reported by several studies. In present study, it is found that the incidence of septicaemia was higher in male babies compared to female babies by 10.5%. Varsha et al[24] reported in their study that 74.6% of neonates evaluated for sepsis are less than 3 days of age and 25.3% are in the late onset group that is greater than 3 days of age. In present study, 51 neonates are age less than or equal to 3 days (72 hours) of age and the rest 54 belonged to the late onset sepsis group that is greater than 3 days of life. In the present study, refusal of feeds, lethargy, respiratory distress, jaundice and convulsions were the main clinical features. Despite the increased availability of innovative molecular technologies for detecting and reporting microbial pathogens most clinicians still consider the isolation of bacteria and antimicrobial susceptibility report as the most important test generated by clinical microbiology laboratory.

In present study, blood culture positivity is observed in 26 (24.76%) neonates. Of these 13 are EOS and 13 are LOS.

Klebsiella is isolated in 50% of culture positive cases followed by Coagulase negative staphylococcus and enterococci. These are sensitive to vancomycin and cefoperazone. Mortality is observed in 16 (15.24%) neonates. Rest of the 89 neonates (84.76%) were discharged with an average duration of hospital stay of 12 days**.**

IV. Limitations:

1. Idiopathic thrombocytoprnia
2. Increased consumption of platelets due to indwelling catherters.

V. Conclusions:

1. In our study significant number of 'at risk neonates' were shown to have thrombocypenia; hence consider doing platelet count in all 'at risk neonates'
2. Neonates with late onset sepsis are slightly higher number than early onset sepsis. This indicates many postnatal factors are playing role in development of sepsis.
3. Male neonates outnumbered female neonates.
4. The main clinical presentation is refusal of feeds followed by respiratory distress, convulsions, lethargy.
5. Klebseilla is the most common organism isolated in the culture followed by staphylococcus and enterococus. These organisms are sensitive to vancomycin and cefoprazone.
6. Mortality is almost equal in EOS as well as LOS.

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