JOURNAL OF CRITICAL REVIEWS

ISSN-2394-5125 VOL1 , ISSUE 1, 2014

CLINICAL CHARACTERISTICS AND ANTIBIOTICS RESISTANCE PATTERNS OF NEWBORN SEPSIS IN TERTIARY CARE HOSPITAL

Dr Saptarshi Bhattacharyya[1*], Dr Uday Rao[2]

[1*](Assistant Professor Paediatrics), Malla Reddy Institute of Medical Sciences, Telangana. India
[2](Associate Professor Paediatrics) Malla Reddy Institute of Medical Sciences, Telangana. India

***Corresponding Author**: Dr Saptarshi Bhattacharyya.
[*](Assistant Professor Paediatrics), Malla Reddy Institute of Medical Sciences, Telangana. India 330 R.N.Tagore.Kolkata : 700077.West Bengal.India

Abstract

Neonatal sepsis (NS) continues to be a significant contributor to illness and death in newborns, although there is a lack of comprehensive information on the causes and antibiotic resistance patterns of the bacteria involved. The purpose of this study was to evaluate the clinical characteristics, risk factors, and the antibiotic susceptibility patterns of pathogenic microorganisms associated with NS at tertiary children's hospital.

A retrospective review was conducted on episodes of blood culture-proven sepsis in the neonatal intensive care unit (NICU) of Children's Hospital of Malla Reddy Institute of Medical Sciences, Telangana. India , covering the period from March 2012 to Dec 2013. The collected data encompassed information on demographics, perinatal risk factors, clinical symptoms, laboratory values, microbiology results, and the susceptibility of the microorganisms to antimicrobial agents. A comparison was made between the data for early-onset newborn sepsis (AEONS) and late-onset neonatal sepsis (LONS).

A total of 170 cases with positive culture results were chosen for analysis. Among these instances, there were 34 cases of early-onset neonatal sepsis (AEONS), 49 cases of late-onset neonatal sepsis (LONS). A total of 635 instances that were not completed were excluded. There were notable disparities in risk factors between the AEONS group and LONS group, including birth weight, gestational age, respiratory assistance, and the utilisation of peripherally inserted central catheter (PICC). There were noticeable variations across the groups in terms of clinical symptoms, including fever, feeding difficulties, abdominal swelling, and infant jaundice. Additionally, there were disparities in test findings, such as haemoglobin and lymphocyte counts. Staphylococcus epidermidis , Escherichia coli , Alcaligenes xylosoxidans and Klebsiella pneumoniae remain the primary pathogens responsible for newborn sepsis. The majority of Gram-positive bacteria isolates shown susceptibility to vancomycin, linezolid, minocycline, and tigecycline, with over 90% demonstrating resistance to penicillin.Better medical decisions, notably early detection and suitable initial antimicrobial therapy can be made after recognising the various clinical characteristics and pathogens of EONS and LONS.

Introduction

Neonatal sepsis (NS) is used to define a systemic disease of bacterial, viral, or fungal (yeast) infection that is linked with hemodynamic abnormalities and other clinical symptoms that result in considerable morbidity and death[1]. A agreement regarding the definition of newborn sepsis has remained elusive. Neonatal sepsis can be categorised into 2 subgroups, early-onset (AEONS) and late-onset (LONS), based upon whether the beginning of symptoms occurs before 72 hours of life or after[2]. AEONS is defined as the initiation of sepsis symptoms within 72 hours of delivery and is caused by bacteria present in the maternal vaginal tract before or at the moment of birth. LONS, which develop 72 hours after birth, are presumably caused by germs spread from the hospital or the community during delivery[3].Early detection and treatment of the newborn with suspected sepsis are critical to avert serious and life-threatening consequences. The diagnosis of neonatal sepsis is complicated due to diverse and non-specific clinical signs, as well as the difficulties of analysing infection indicators in the early stages[4]. In clinical practice, therapy is hindered by the lack of sensitivity of bacterial cultures and the lack of appropriate diagnostic markers[5]. Antibiotic therapy is also progressively hampered by the growth of bacterial resistance, which has become a significant concern in various nurseries across North America[6]. India has a huge geographical area, and the frequency and distribution of diseases varies greatly throughout the country. It is crucial to establish the common infections and related therapeutic susceptibilities for particular hospitals. In addition, it is vital to actively monitor the local epidemiology of newborn sepsis to detect any changes in infection patterns and medication susceptibility[7].The objective of this article was to investigate the bacterial pathogens, to analyse the associated risk factors, and to confer the antibiotic susceptibility pattern of common causative pathogens of neonatal sepsis in the Children's Hospital of Malla Reddy Institute of Medical Sciences, Telangana. India , which may provide guidance on empirical antimicrobial treatment for neonatal sepsis.

ISSN-2394-5125 VOL1 , ISSUE 1, 2014

Methods

The Children's Hospital Ethics Committee of Malla Reddy Institute of Medical Sciences, Telangana. India gave its approval for this retrospective cohort research, which was carried out between March 2012 to Dec 2013. In patients with clinical and laboratory signs consistent with infection, neonatal sepsis was defined as the development of a single potentially pathogenic organism (bacterium or fungal) from blood or cerebrospinal fluid (CSF)[8].

Inclusive criteria: neonates (0–28 days) present with the risk factors and clinical signs of sepsis at the time of admission or who acquired sepsis during hospitalisation were included in this research. Exclusion criteria: among 565 culture-positive newborns, 264 instances with incomplete data were eliminated[9].

Subgroups of early-onset newborn sepsis (AEONS, beginning of symptoms before 72 hours of life) and late-onset neonatal sepsis (LONS, onset of symptoms after 72 hours after birth and before 28 days) were created from the 170 cases that were found to be eligible. Patient medical records comprising clinical symptoms, haematological markers, pathogenic characteristics, and antimicrobial susceptibility were evaluated. Each patient's data was collected using a uniform data collecting form. Blood cultures were taken from neonates with risk factors and clinical symptoms indicative of sepsis. All blood samples were taken prior to the beginning of antimicrobial medication. To establish if the organism is an actual disease or a contaminant, a repeat blood culture was necessary. If the patient had 2 consecutive positive blood cultures, the neonatal sepsis was diagnosed. A few babies suffered more than one bout of sepsis. If the blood culture was remained positive following 10-day suitable antimicrobial therapy or a new organism was detected from a second culture, it was termed an additional episode.The antibacterial susceptibility for isolated microorganisms was assessed[9]. Antimicrobial susceptibility testing of isolated pathogens was done using the ATB susceptibility system by the Kirby Bauer disc diffusion technique according to Clinical and Laboratory Standards Institution (CLSI) standards.

Statistics

SPSS 19.0 for Windows (IBM, Armonk) was used to evaluate the data after it was input in Microsoft Excel 2010. The distribution disparities of categorical variables were analysed using the Mantel-Haenzel chi-square test or Fisher exact test according to the necessity of the issues. To compare the Apgar score between 2 groups, an independent sample t test was performed. A two-sided P value of.05 was judged statistically significant. This retrospective investigation was undertaken with consent from the Ethics Committee of our college. Due to the retroactive nature of the investigation, informed consent was waived.

Table 1 Clinical finding of our study in EONS and LONS

	Clinical parameters	**Total (%)**	**EONS (%)**	**LONS (%)**	**P**
1	Gender				0.74
	Male	61.02	28.91	39.54	
	Female	48.24	36.87	55.36	
2	Mode of delivery				
	Vaginal delivery	51.36	44.25	58.36	0.41
	Caesarean section	53.44	53.64	48.35	
3	Gestational age (weeks)				
	Extreme preterm < 28	8.65	13.25	5.44	0.0001
	Very preterm 28 to 32	21.55	38.88	70.22	0.0001
	Moderate/late preterm 32 to 37	28.99	36.22	21.54	0.001
	Full-term *>37*	55.24	16.22	65.77	0.001
4	Birth weight (g)				
	>2500	45.44	26.33	61.87	0.001
	1500 to 2500	14.11	35.44	19.74	0.001
	1000 to 1500	15.22	26.78	9.55	0.002
	<1000	16.22	14.55	5.47	0.001
5	Premature rupture of membrane	17.22	16.34	12.78	0.005
6	Polluted amniotic fluid	10.89	15.45	8.98	0.02
7	Umbilical cord around neck	7.88	5.47	8.97	0.48
8	Duration of hospital stay (d)	21±2.05	16±5.45	13±8.59	
9	Antibiotic treatment lasted (d)	19±4.22	15±2.45	12±9.65	
10	Fever	36.22	14.58	54.22	0.001

11	Feeding intolerance	45.12	35.21	41.77	0.005
12	Respiratory distress	15.01	46.28	3.89	0.02
13	Neonatal jaundice	45.12	61.47	21.59	0.005
14	Hypoglycemia	10.24	15.56	6.58	0.02
15	Neonatal asphyxia	15.47	21.48	3.98	0.02
16	Pulmonary hypertension	9.64	16.56	3.87	0.02
17	Respiratory failure	8.97	11.58	6.54	0.02
18	White blood cell counts (<8 or >12) $^{*}10^{9}$/L	71.45	78.32	68.11	0.001
19	Lymphocyte counts (<0.8 or >4) $^{*}10^{9}$/L	38.45	25.22	49.33	0.005
20	C-reactive protein (>8) *mg/L	29.24	16.45	39.47	0.005
21	Neutrophil counts (<0.8 or >4) $^{*}10^{9}$/L	51.44	69.24	57.22	0.001
22	Platelet counts (<100 or >300) $^{*}10^{9}$/L	36.33	17.55	47.29	0.005
23	Hemoglobin (<110 or >160) *g/L	56.44	69.22	48.34	0.005
24	Procalcitonin (>0.05) *ng/mL	97.37	98.64	98.45	0.005
25	Gram-positive pathogens	55.11	41.24	69.35	0.005
26	CoNS	71.48	78.36	61.49	0.005
27	Staphylococcus haemolyticus	10.78	18.75	6.97	0.05
28	Staphylococcus capitis	15.26	19.88	7.47	0.005
29	Staphylococcus hominis	16.54	9.87	19.54	0.005
30	Other CoNS	10.24	5.65	13.47	0.05
31	Staphylococcus aureus	9.87	5.46	8.78	0.01
33	Enterococcus faecalis	41.22	54.13	36.87	0.004
35	Streptococcus spp.	15.24	12.47	14.98	0.02
36	Gram-negative pathogens	36.21	39.54	28.47	0.005
39	Alcaligenes xylosoxidans	28.41	45.14	7.87	0.005
40	Serratia spp	1	0	0	
41	Pseudomonas spp.	15.23	19.74	9.64	0.005
42	Acinetobacter spp.	0	0	1	
43	Enterobacter spp.	2	2	3	
44	Other gram-negative pathogens	0	1	2	
45	Fungi	11.47	16.34	5.48	0.02
47	Candida pelliculosa	27.65	31.47	29.87	0.002

Results

Occurrence rates of NS and risk factors

This was a retrospective examination of hospital data from March 2012 to Dec 2013. Among 5421 newborns admitted to the NICU, 348 neonates were diagnosed with neonatal sepsis. Of the 348 newborns with clinical neonatal sepsis, 319 and 434 obtained positive and negative culture findings, respectively. For further analysis, instances with missing data were removed, and 170 cases were chosen, which comprised 34 AEONS cases and 49 LONS cases. Among these culture-

ISSN-2394-5125 VOL1 , ISSUE 1, 2014

proven septic neonates, the percentage of full term delivery (>37 weeks), normal birth weight (>2500 g), and high Apgar score were greater in the LONS group than in the AEONS group. The proportion of preterm birth, low birth weight, premature rupture of membrane, polluted amniotic fluid, need for respiratory support, use of a peripherally inserted central catheter (PICC), duration of hospitalisation, and antibiotic treatment was higher in the AEONS group than that in the LONS group. (Table 1).

Clinical signs and haematological markers of neonatal sepsis

Respiratory distress (46%), newborn jaundice (61%), hypoglycemia (15%), pulmonary hypertension (16%), and neonatal asphyxia (21%) were the most prevalent clinical symptoms of AEONS according to the data. In contrast, fever (54%) and eating intolerance (41%), and happened more regularly in the LONS group. We analysed the proportion of cases with abnormal hemograms in the AAEONS and LONS groups, respectively, and found that abnormal neutrophil counts and haemoglobin concentrations were more common in the AAEONS group, while abnormal lymphocyte counts, C-reactive protein (CRP), and platelet counts were more common in the LONS group. These clinical signs might be useful in achieving a more accurate early diagnosis and lowering the burden of illness caused by misdiagnosis and delayed diagnosis. Other clinical measures, including hypotonia/poor activity, respiratory failure, white blood cell (WBC) counts, and procalcitonin (PCT), indicated no significant statistical difference between the AEONS and LONS groups (Table 1). The major pathogenic bacterium in NS was Gramme-positive bacteria, which accounted for 41% and 72% of all infections in the AEONS and LONS groups, respectively. Coagulase-negative staphylococcus (CONS) was the most frequent Gramme-positive bacterium, accounting for 54 and 45% in the AEONS and LONS groups, respectively. Gramme-negative pathogens accounted for 46% and 35% of all infections in the AAEONS and LONS groups, respectively, with Escherichia coli appearing most often in the LONS group (56%) and Alcaligenes xylosoxidans happening most regularly in the AAEONS group (31%). Fungal pathogens (11.%) were relatively infrequent compared to bacteria, yet they caused 19% of all AEONS cases and 6% of all LONS cases.

A significant degree of resistance to popular first- and second-line antimicrobials was identified for the principal causal microorganisms of NS. Gramme-positive bacteria exhibited a high sensitivity rate to the following drugs: tigecycline, linezolid, and vancomycin None of the 32 strains of A. xylosoxidans were resistant to tigecycline (100.00%), levofloxacin (100.00%), meropenem (100.00%), and cefoperazone/sulbactam (100.00%). None of the 33 strains of E. coli were resistant to ertapenem (100.00%), cefmetazole (100.00%), meropenem (100.00%), and amoxicillin/clavulanic acid (100.00%). The susceptibility rate to following medications was high among Klebsiella spp.: amikacin (100.00%), levofloxacin (100.00%) and gentamicin (80.65%) (Table 1).

Discussion

Because it can be tough to identify NS from other neonatal illnesses based purely on clinical indications, especially in the early stages, the diagnosis of NS is complex.Blood and cerebrospinal fluid (CSF) culture has been accepted as the gold standard for identifying bacterial sepsis. However, body fluid culture is time-consuming because pathogens of NS are widely dispersed. Besides, the total culture positive rate was 28% in our study, which was lower than that in previous publications[1,10,11]. Therefore, for the early identification and treatment, it is vital to continue to investigate risk factors, clinical symptoms, related diagnoses, pathogenic microorganisms and antimicrobial susceptibility of neonatal sepsis. By evaluating and measuring the risk factors in the perinatal age, we can better differentiate the diagnosis of EONS and LONS[12,13]. Preterm delivery, low birth weight, preterm rupture of membrane, and amniotic fluid-contaminated neonates were more prevalent among validated EONS cases, which resulting in larger rate of breathing help and PICC, and longer period of hospitalization and antibiotic therapy[14,15]. In comparison, most newborns with LONS were characterized by normal birth weight, full-term delivery, and higher Apgar score. A study of babies with EONS in the UK found that risk factors were present in 78% instances, yet in almost half (17 of 35) of the cases, the only predictor was preterm labor. Another study categorised LONS into community-acquired (neonates admitted from home) and hospital-acquired (neonates had infections in the NICU and blood culture was done before administration of antibiotics) categories[16,17 &18]. There was no significant difference in clinical features between the 2 groups, while the hospital-acquired LONS infants were more likely to be preterm. Compared with this research, most LONS cases in our inquiry were community-acquired, among which risk factors were quite infrequent[19&20]. Gender, way of birth and nuchal cord revealed no variation between 2 groups in our experiment, which was consistency with previous publications[11,19&20].

Early beginning of antimicrobial treatment is typically delayed because the early clinical signs of sepsis are non-specific. In our analysis, we noticed that clinical signs in order of frequency were newborn jaundice, feeding intolerance, hypotonia/poor activity, fever, and respiratory distress. These findings were comparable to earlier study[21,22&23]. The incidence of respiratory distress, newborn jaundice, hypoglycemia, neonatal hypoxia and pulmonary hypertension was greater in EONS group than that in LONS group, whereas fever, feeding intolerance and abdominal distension were more prevalent in LONS group. The clinical signs of EONS and LONS were unique because of the reasons and the date of start and the pace of progression. The differences we observed were based on the assumption that early- onset infections were presumably transmitted perinatally from the mother and late-onset infections were acquired postnatally from an environmental source/20-24] which resulted in differences of symptom severity, pathogen distribution, and antibiotic susceptibility[24&25]. Therefore, it is crucial to recognise the early clinical signs and decrease the prevalence of underdiagnoses and misdiagnosis

ISSN-2394-5125 VOL1 , ISSUE 1, 2014

In clinical practice, numerous test data such as CRP, WBC counts, lymphocytes, and neutrophils are typically utilised to support the diagnosis of sepsis. We discovered that the levels of PCT, WBC counts, and haemoglobin are more likely to be abnormal compared with C-reactive protein and platelet counts. However, other studies believed CRP to be an indication of both sensitivity and specificity[12 &18]. They evaluated a CRP value >10 mg/L paired with a neutrophil ratio >0.25 as a criteria for beginning antibiotic treatment. In our study, the proportion of aberrant neutrophil counts and haemoglobin significantly greater in AEONS, while lymphocyte counts, CRP value, and platelet counts were more beneficial in diagnosing LONS[4,5,&23]. There is no unanimity on haematological parameters; its findings are impacted by the health state of the perinatal mother and her medications, age of onset, and usage of antibiotics in neonates. A recent study demonstrated that although CRP may be raised in newborns, CRP was not an accurate diagnostic in picking up instances[24]. Therefore, haematological characteristics may only be used as an auxiliary tool for diagnosis, not such a "gold tandard." Grammeme-positive infection was shown to be more prevalent than Grammeme-negative and fungal. CoNS was the predominant gramme-positive pathogen for both AEONS and LONS, which was consistent with earlier investigations in Asia and other developing nations. However, real bacteremia produced by coagulase-negative Staphylococcus is difficult to identify from blood culture contamination. Another pathogen, GBS, is highly prevalent in international studies but relatively rare in India, which was consistent with previous mainland India findings and may be connected to the low prevalence of GBS colonisation in Chinese pregnant women[16, 21 &23]. With the evolution of perinatal medicine and neonatal first-aid technologies, the survival rate of preterm newborns, especially very/extremely low birth weight (VLBW/ELBW) infants, has been rising year by year. Because the overall state of these neonates is generally poorer, invasive surgeries such as tracheal intubation and arteriovenous catheterization are commonly necessary. CoNS can create biofilm and are likely to attach to medical devices. CoNS infection is a major risk factor for preterm newborns. However, CoNS are natural flora of the human skin and mucosa whose toxicity has long been disregarded, and few systematic research were left explaining their epidemiology in human infections. Nevertheless, colonised CoNS bacteria have been documented to be causative for human infections, particularly in immunocompromised hosts, including newborns. The immune system of newborns is young, and the skin and mucous membranes are too sensitive to provide an effective physical barrier. Relying on antibodies from mothers, newborns may fight against harmful microbes. Due to the potential false-negative results by multiple tests, empirical therapy for newborn sepsis needs to be begun in suspected instances. An optimum choice of antimicrobial drugs is to cover the most frequent infections without creating selection pressure for antibiotic resistance[20 &25]. Currently, the recommended first-line treatment comprises gentamicin+flucloxacillin and genta- micin+amoxicillin/penicillin. This may be suitable in the UK or other Western nations. However, in reports from many other nations or areas, distinct patterns of causal microorganisms have been detected, and the first-line medication should be changed according to local epidemiology. Although the resistance rate of several Gramme-positive bacteria to gentamicin, rifampicin, levofloxacin, and ciprofloxacin is low, these antibiotics may have serious negative effects on liver, kidney, hearing, and cartilage development, which makes them an undesirable choice for neonates. Vancomycin, a glycopeptide antibiotic, is the most effective and cheap medication for treatment of staphylococcal infections. However, vancomycin-resistant Staphylococcus has been observed; the sensible use of vancomycin is of major relevance in minimising and/or deferring the formation of vancomycin-resistant strains[17 &20]. The risk for fungal sepsis is raised by colonisation acquired vertically from maternal sources as well as horizontally from the NICU environment. The incidence rate of fungal infection in infants was reported to be 10%. We should be vigilant and take specific prophylactic to decrease the average duration of hospitalisation, standardise the usage and dose of antibiotics, prevent invasive surgeries, and enhance the complete diagnosis and treatment in the NICU to limit the risk of infection.

Our study has significant limitations. It was a descriptive research, thus additional examination of the connection with potential risk variables was not feasible. Due to the inclusion and exclusion criteria constraints, the AEONS group may include a few hospital-acquired LONS patients, resulting in a variation in clinical parameters between the two groups. When assessing haematology data, the proportion of neutrophils and lymphocytes is more important than the absolute value, and the 95% confidence interval (CI) of these values should be changed based on the age.

In conclusion, S. epidermidis, E. coli, A. xylosoxidans, and K. pneumoniae remain to be the predominant organisms responsible for newborn sepsis at the tertiary children's hospital. Better medical judgements on first antimicrobial therapy, based on early detection, may be made after a continual updated understanding of the clinical characteristics and pathogens of AEONS and LONS.

Conflict of interest- NO

References

1. World Health Organization: Essential Newborn Care**.** In *A report of a Technical Working Group* WH0 Geneva; 1995.
2. Siegel JD, McCraken GH: Sepsis neonatorum**.** *N Engl J Med* 1981, 304:642-7.
3. Yurdakok M: Antibiotic use in neonatal sepsis**.** *Turk* 1998, 40(1):17-33.
4. French GL: : Clinical impact and relevance of antibiotic resistance**.** *Advanced Drug Delivery Reviews* 2005, 57:1514-1527.
5. English M, Ngama M, Mwalekwa L, Peshu N: Sign and Symptoms of illness in Kenyan Infants aged less than 60 days**.** *Bulletin of the WHO* 2004, 82:323-329.

ISSN-2394-5125 VOL1 , ISSUE 1, 2014

6. The WHO Young Infants Study Group: Clinical predilection of serious bacterial infection in young infants in developing countries**.** *Pediatr Infect Dis J* 1999, 18:s23-31.
7. Tumbarello M, Sanguinetti M, Montuori E, Trecarichi M E, Posteraro B, Fiori B, Citton R, D'Inzeo T, Fadda G, Cauda R, Spanu T: : Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended- Spectrum-Lactamase-Producing Enterobacteriaceae: Importance of Inadequate Initial Antimicrobial Treatment**.** *Antimicrob Agents Chemother* 2007, 51:1987-1994.
8. Weber MW, Carlin JB, Gatchalian S, Lehmann D, Muhe L, Mulholland EK, WHO Young Infants Study Group: Predictors of neonatal sepsis in developing countries**.** *Pediatr Infect Dis J* 2003, 22(8):711.
9. Klingenberg C, Olomi R, Oneko M, Sam N, Langeland N: Neonatal morbidity and Mortality in Tanzanian tertiary care referral hospital**.** *Ann of Trop Paediatr* 2003, 23:293-299.
10. Iregbu KC, Elegba OY, Babaniyi IB: Bacteriological profile of neonatal septicemia in a tertiary Hospital in Nigeria**.** *Afr Health Sci* 2006, 6(3):151-154.
11. Mugalu J, Nakakeeto MK, Kiguli S, Kaddu-Mullindwa DH: Aetiology, risk factors and immediate outcome of bacteriologically confirmed neonatal septicaemia in Mulago hospital, Uganda**.** *Afr Health Sci* 2006, 6:120-126.
12. Singh SA, Dutta S, Narang A: : Predictive clinical scores for diagnosis of late onset neonatal septicemia. *J Trop Pediatr* 2003, 49(4):235-9.
13. Bradford PA: Extended spectrum beta lactamases in the 21st century: Characterization epidemiology and detection of this important resistance threat. *Clin Microbiol rev* 2001, 14:933-951.
14. Stoll BJ: The global Impact of neonatal infections. *Clin Perinatol* 1997, 24:1-21.
15. Murray Baron, Pfaller Tenover: Manual of Clinical Microbiology. 6th edition. American Society of Microbiology Press, Washington DC; 1999.
16. Clinical and Laboratory Standards Institute: Performance standards for antimicrobial disk susceptibility tests. Approved standard. In *Ninth edition Document M2-A9* Clinical and Laboratory Standards Institute, Wayne, PA; 2006.
17. SPSS Inc version 13.0: *Statistical Package for the Social Sciences* Chicago, II: SPSS Inc; 2004.
18. M'Zali FH, Chanawong A, Kerr KG, Birkenhead D, Hawley PM: Detection of extended-spectrum beta-lactamases in members of the family Enterobacteriaceae: comparison of the Mast DD test, the double disc and the E-test ESBL. *Antimicrob Agent Chemother* 2000, 45:881-5.
19. Kudawla M, Dutta S, Narang A: Validation of a clinical score for the diagnosis of late Onset neonatal septicaemia in babies weighing 10002500 g. *J Tropic Pediatr* 2008, 54:66-69.
20. Tallur SS, Kasturi AV, Nadgir SD, Krishna BVS: Neonatal septicemia in Hubii. *Indian J Pediatr* 2000, 67:170-174.
21. Jain A, Roy I, Gupta MK, Kumar M, Agarwal SK: Prevalence of extended- spectrum-lactamase producing Gram-negative bacteria in septicaemic neonates in a tertiary care hospital. *J Med Microbiol* 2003, 52:421-425.
22. Tessin I, Trollfors B, Thlringer K: Incidence and etiology of neonatal septicemia and meningitis Western Sweden. *Acta Pediatr Scand* 1990, 79:1023-30.
23. Bloomberg B, Jureen R, Manji KP, Tamim BS, Mwakagile DSM, Urassa WK, Fataki M, Msangi V, Tellevik MG, Maselle SY, Langeland N: High Rate of Fatal Cases of Pediatric Septicemia Caused by Gram-Negative Bacteria with Extended-Spectrum Beta-Lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol* 2005, 43(2):745-749.
24. Saez-Llorens GH McCracken: Sepsis syndrome and septic shock in Pediatrics. Current concepts of terminology, pathophysiology and management. *J Pediatr* 1993, 123:497-508.
25. Monga K, Fernandez A, Deodhar L: Changing bacteriological patterns in neonatal septicemia. *Indian J Pediatr* 1986, 53:505-508