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Original Research Article

Clinical and bacteriological study of neonatal septicaemia in a tertiary care hospital

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ABSTRACT

Background: Neonatal sepsis is a clinical syndrome of bacteraemia characterized by systemic signs and symptoms in the first month of life. It is the leading causes of neonatal mortality and morbidity. Early diagnosis and treatment with appropriate antibiotics is important to improve the prognosis of neonatal sepsis. Our objectives were to study the organisms causing neonatal septicaemia, associated risk factors, to correlate CRP with blood culture and to study mortality rate in neonatal septicaemia.
Methods: The study of 2 years included clinically suspected cases of neonatal septicaemia admitted in NICU. 566 blood samples were collected, processed and isolates were identified. Maternal and neonatal risk factors were studied. CRP test was done by slide agglutination test.
Results: Blood culture was positive in 205 (36.22%) cases. Among the culture positive cases, 128 (62.44%) were males and 77 (37.56%) females with male to female ratio of 1.66:1. Early onset sepsis was present in 137 (66.83%) and late onset sepsis in 68 (33.17%) cases. 107 (52.20%) were low birth weight babies. The most common neonatal risk factor was prematurity 75 (36.58%) and maternal risk factor was prolonged rupture of membrane 65 (31.71%). gram negative bacilli 144 (70.24%) were found to be common cause of sepsis than gram positive cocci 61 (29.76%), *Klebsiella pneumoniae* 54 (26.34%) being most common pathogen. Out of 566, CRP test was positive in 244 (43.10%) cases. Mortality rate was 23.41%.
Conclusions: Neonatal septicaemia is a life-threatening emergency. The study of etiological profile and CRP test plays a significant role.

Keywords: Blood Culture, CRP, Neonatal, Septicaemia

INTRODUCTION

Neonatal sepsis is a clinical syndrome of systemic illness accompanied by bacteremia occurring in the first month of life.[1] The immaturity of immune system in the neonates makes them especially susceptible to infections during the neonatal and perinatal period. Neonatal septicaemia is by far the most important and often fatal sequelae of such infection.[2] In India it is commonest cause of neonatal mortality contributing to 38% of the neonatal deaths.[3] For epidemiological and therapeutic purposes, neonatal septicaemia is categorised into early onset neonatal septicaemia (EONS), which presents within the first 72 hours of life and late onset neonatal septicaemia (LONS) presenting after 72 hours of life.[1] This distinction has clinical relevance, as early onset neonatal sepsis is generally acquired from pathogens of maternal genital tract, whereas late onset sepsis has its origin either from the community or from hospital.[4]

In neonatal sepsis numerous neonatal, maternal and environmental risk factors contribute to the high

morbidity and mortality. The various risk factors which are associated with EONS are low birth weight (<2500gms), preterm baby, febrile illness in the mother, foul smelling and/or meconium stained liquor amnii, prolonged rupture of membrane (>24 hours), more than 3 vaginal examinations during labor, prolonged and difficult delivery with instrumentation, perinatal asphyxia or difficult resuscitation. Whereas the risk factors for development of LONS include prolonged NICU admission, poor hygiene, low birth weight (LBW), poor cord care, prematurity, bottle feeding, invasive procedure, superficial infection (pyoderma, umbilical sepsis), prelacteal feeding, ventilation, aspiration of feeds etc.[5]

Early diagnosis is a key to reduce morbidity and mortality of neonatal septicaemia. The gold standard for diagnosis of septicaemia is the isolation of bacterial agents from the blood culture. But definitive culture results take at least 48-72 hours resulting in treatment delays. Hence two-pronged approach is used for the evaluation of neonates with possible sepsis. Nonspecific sepsis screen tests like C-reactive protein (CRP), erythrocyte sedimentation rate, total white blood cell count and absolute neutrophil count are used to evaluate the likelihood of infection, and specific diagnostic tests are performed to confirm the presence of a specific pathogen in body fluids.[6]

Both gram negative and gram-positive bacteria have been isolated from blood. Organisms causing sepsis and their susceptibility to different antibiotics vary from place to place. As neonatal septicaemia is life threatening emergency, early diagnosis and treatment with appropriate antibiotics is necessary. Study objective was to study the organisms causing neonatal septicaemia in our region, risk factors associated with neonatal septicaemia, to correlate CRP with blood culture and to study the mortality rate in neonatal septicaemia.

METHODS

The observational study of 2 years was carried out from April 2014 to March 2016, in the department of microbiology, Indira Gandhi government medical college, Nagpur. Clinically suspected cases of neonatal septicaemia admitted in neonatal intensive care unit (NICU) were included in the study. Prior to collection of blood sample, consent from mother was taken and detailed history of each neonate along with history of maternal risk factors, neonatal risk factors and mode of delivery etc, was recorded.

Blood culture[7]

The skin of venepuncture site was disinfected with 70% alcohol and 1% iodine for at least 1 minute and allowed to dry. With precaution to avoid touching and contaminating venepuncture site, 2 ml of blood was withdrawn with disposable needle and syringe and inoculated into blood culture bottle containing 20 ml of trypticase soy broth. The blood and broth were mixed gently; the bottles were transported immediately to laboratory and incubated at 37°C aerobically. First subculture was done after 6-17 hours on 5% sheep blood agar and Mac Conkey agar plates. Thereafter daily subculture was done for 7 days. The isolates were identified by Gram staining, colony characteristics and biochemical properties. Cultures were labelled negative if there was no growth after 1 week of incubation. Antimicrobial susceptibility of all bacterial isolates was done by Kirby-Bauer disk diffusion technique as per CLSI 2014 guidelines.[8,9]

C-Reactive protein (CRP) test

For CRP testing, 2 ml Blood samples was collected and serum was separated. Testing was done by slide agglutination test according to manufacturer's instructions (Tulip diagnostics (P) Ltd).

Statistical analysis

Statistical analysis was done by chi square test and Mc-Nemar Chi-square test. p value <0.05 was considered as statistically significant.

RESULTS

Out of total 566 blood samples subjected for culture, 205 (36.22%) were culture positive and 361 (63.78%) were culture negative. The culture positivity rate was 36.22%. Out of total 205 culture positive cases 137 (66.83%) were of age less than 3 days belonging to early onset septicaemia, while 68 (33.17%) cases were between the age of 3 days to 28 days belonging to late onset septicaemia (Table 1). Among them 128 (62.44%) were males and 77 (37.56%) were females with male to female ratio of 1.66:1.

Table 1: Age wise distribution of culture positive cases (n=205).

Age (days)	No of cases	Total (%)
0-3	137	137 (66.83) EONS
4-6	8	68 (33.17) LONS
7-9	4	
10-12	12	
13-15	5	
16-18	12	
19-21	8	
22-24	10	
25-28	9	
0-28	205	205 (100)

Table 2 shows birth weight wise distribution of the cases. Out of the total 205 culture positive neonates, maximum neonates 107 (52.20%) were low birth weight babies. The most common neonatal risk factor responsible for the infection was prematurity in 75 (36.58%) neonates,

followed by respiratory distress in 70 (34.15%) neonates (Table 3).

Table 2: Birth weight wise distribution of culture positive cases (n=205).

Neonatal birth weight	No. of culture positive (%)
Normal birth weight (≥2500g)	53 (25.85)
Low birth weight (<2500g)	107 (52.20)
Very low birth weight (<1500g)	45 (21.95)
Extremely low birth weight (<1000g)	0
Total	205 (100)

Table 3: Neonatal risk factors among culture positive cases (n=205).

Risk factors	Culture positive cases (%)
Prematurity	75 (36.58)
Respiratory distress	70 (34.15)
Parenteral nutrition	57 (27.80)
Mechanical ventilation	52 (25.36)
Birth asphyxia	07 (03.36)

Table 4 shows maternal risk factors. Mothers of 65 (31.71%) neonates had history of prolonged rupture of membrane (PROM) and maternal fever was seen in 23 (11.22%). Of the total 205 culture positive neonates, total 105 (51.22%) were delivered in hospital while 15 (07.31%) were delivered at home by normal vaginal delivery. Lower segment caesarean section (LSCS) was the mode of delivery in 65 (31.71%) cases and instrumentation was used in mothers of 20 (09.76%) neonates (Table 5).

Table 4: Maternal risk factors among culture positive cases (n=205).

Risk factors	Culture positive cases (%)
Prolonged rupture of membrane	65 (31.71)
Maternal fever	23 (11.22)

Table 5: Distribution of culture positive cases as per mode of delivery (n=205).

Mode and place of delivery	Culture positive cases (%)
Normal vaginal delivery at hospital	105 (51.22)
Normal vaginal delivery at home	15 (07.31)
Lower segment caesarian section (LSCS)	65 (31.71)
Instrumentation	20 (09.76)
Total	205 (100)

Table 6 shows the isolates from blood culture of neonatal septicaemia cases. Gram negative bacilli 144 (70.24%) were common etiological agents as compared to gram positive cocci 61 (29.76%). The most common gram-negative organism causing sepsis was *Klebsiella pneumoniae* 54 (26.34%) and gram-positive organism was *S. aureus* 36 (17.56%).

Out of total 137 EONS cases, gram negative bacilli were 103 (75.18%) and gram-positive cocci were 34 (24.82%). Of them, Klebsiella pneumoniae 44 (32.12%) was the commonest isolate. In LONS cases (68), gram negative bacilli 41 (60.29%) predominated as compared to gram positive cocci 27 (39.71%) and the most common pathogen was *S. aureus* 22 (32.35%).

Table 6: Distribution of organisms as per the onset of septicaemia.

Organisms isolated	EONS (%)	LONS (%)	Total (%)
Gram negative organisms	103 (75.18)	41 (60.29)	144 (70.24)
Klebsiella pneumonia	44 (32.12)	10 (14.71)	54 (26.34)
Pseudomonas aeruginosa	11 (08.03)	16 (23.53)	27 (13.17)
Escherichia coli	20 (14.59)	03 (04.41)	23 (11.22)
Acinetobacter baumannii	04 (02.92)	10 (14.71)	14 (06.83)
Enterobacter spp	08 (05.84)	00 (0)	08 (03.90)
Citrobacter spp	08 (05.84)	00 (0)	08 (03.90)
Klebsiella oxytoca	06 (04.38)	00 (0)	06 (02.93)
Acinetobacter lwoffii	02 (01.46)	02 (02.94)	04 (01.95)
Gram positive organisms	34 (24.82)	27 (39.71)	61 (29.76)
Staphylococcus aureus	14 (10.22)	22 (32.35)	36 (17.56)
CONS	14 (10.22)	04 (05.88)	18 (08.78)
Enterococcus faecalis	04 (02.92)	01 (01.47)	05 (02.44)
Streptococcus pneumoniae	02 (01.46)	00 (0)	02 (00.98)
Total	137 (100)	68 (100)	205 (100)

Selection of antibiotics and study of sensitivity pattern of the isolates was done as per CLSI guidelines.[9] The most predominant isolate *Klebsiella pneumoniae* was 54 (100%) resistant to Ampicillin and Cefazolin, while they were sensitive to Imipenem 52 (96.30%) and Amikacin 45 (83.34%). All 27 (100%) isolates of *P. aeruginosa* were sensitive to Polymyxin B and *Colistin. Acinetobacter spp* (n=18) showed least resistance to Imipenem (27.78%) and Amikacin (33.33%).

Amongst gram positive organisms, *S. aureus* showed resistance to Penicillin, Cefoxitin, Erythromycin, Gentamycin and Amikacin (94.44%, 52.78%, 41.67%, 33.33% and 16.67% respectively). 52.78% of the Staphylococcus aureus were methicillin-resistant *S. aureus* (MRSA). All the 36 isolates of *S. aureus* and 18 isolates of CONS were 100% sensitive to Vancomycin and Linezolid. Among *Enterococcus faecalis* (n=05), maximum resistance of 60% was seen to Penicillin and Ampicillin and were 100% sensitive to high level Gentamycin, Vancomycin and Linezolid.

CRP test was performed in all 566 clinically suspected cases of septicaemia and its correlation with blood culture was studied. Out of 566 cases, CRP was positive in 244 (43.10%) and negative in 322 (56.90%) cases. Table 7 shows, out of 205 culture positive cases, 198(96.59%) were CRP positive and 07 (3.41%) were CRP negative while out of 361 culture negative cases, 46 (12.74%) were CRP positive and 315 (87.26%) were CRP negative, with a significant p value. Sensitivity and specificity of the CRP test was 96.59% and 87.26% respectively.

Table 7: Correlation of CRP with blood culture positivity (n=566).

CRP test	Blood culture		Total
	Culture positive	Culture negative	
Positive	198 (96.59%)	46 (12.74%)	244
Negative	07(3.41%)	315 (87.26%)	322
Total	205 (100%)	361 (100%)	566

Mc-Nemar Chi square test used, p=8.46×10-8 (p=0.000).

Table 8 shows the mortality of neonates with respect to onset of septicaemia. Out of 137 EONS cases 35 (25.54%) and 68 LONS cases 13 (19.11%) were died of septicaemia. Overall mortality rate was 23.41%. The statistical difference in the mortality rates between two types of septicaemia was not significant.

Table 8: Mortality of culture positive cases as per the onset.

Onset	Culture positive cases	Mortality (%)
Early onset neonatal septicemia	137	35 (25.54)
Late onset neonatal septicemia	68	13 (19.11)
Total	205	48 (23.41)

DISCUSSION

Blood culture results

Blood culture has been regarded as the gold standard for the confirmation of sepsis. In the present study, blood culture positivity in neonatal septicaemia cases was 36.22%. There is wide variation in the culture positivity worldwide ranging from 5% to 60.4%.[10,11] These variations may be due to differences in predisposing factors and infection control practices in the different centres. Our findings were similar to the prevalence rate of 37.69% and 32% reported by Sharma CM et al and Gandhi S et al respectively from India.[12,13] This may be indicative of relatively similar management practices, hospital facilities and services provided. However, Jyothi P et al and Mhada TV et al reported lower prevalence of 19.2% and 24% respectively.[14,15] Low blood culture isolation rate could be due to administration of antibiotic before blood collection from the primary centres or the possibility of infection with anaerobes. A negative blood culture does not exclude sepsis due to anaerobes.[16] Bukhari and Alrabiaah reported a much lower prevalence of 5% in Saudi Arabia which was postulated to be due to the very aggressive clinical management of infants presenting with apparent sepsis.[10]

Age wise distribution of cases

In the present study, 137 (66.83%) neonates were of age less than 3 days belonging to EONS, while 68 (33.17%) were between the age of 3 days to 28 days belonging to LONS (Table 1). Our findings were in accordance with Peterside O et al and Muley VA et al, who found EONS in 66% and 66.7% cases respectively and LONS in 34% and 33.3% cases respectively.[17,18] Jyothi P et al found EONS (74.8%) three times higher than LONS (25.2%).[14] The clustering of these almost 2/3rd cases within 72 hours of life reflects the immaturity of immunological responses in newborn.[18] The EONS occurs due to ascending infection from infected birth canal or following rupture of membrane usually caused by Gram-negative organisms acquired after birth from human contact. In the present study, mothers of 31.71% neonates had history of prolonged rupture of membrane. This may be the reason for EONS to be more common than LONS. Vertically acquired infection from the maternal genital tract emphasize the urgent need to prevent early onset sepsis by promoting clean delivery practices, good antenatal and perinatal care and the use of antibiotic prophylaxis for high-risk mothers during the peri-partum period.

Sex wise distribution of the cases

In the present study, male cases outnumbered the female cases with ratio of 1.66:1. Similar observation was made by Peterside O et al and Jyothi P et al.[14,17] Sexual dimorphism from the human immune response is quite clear. Khatua SP et al postulated that the factors regulating the synthesis of gamma globulins are probably

situated on the X chromosome.[19] Presence of one X chromosome in male infants thus confers less immunological protection compared to female counterpart.

Birth weight

In the present study, 52.20% neonates were having low birth weight. In recent years, there has been a lot of improvement in medical facilities and as a result, the survival rate of the preterm and LBW babies has improved. But at the same time, these neonates with immature immune defences are exposed to NICU flora for a longer duration. Most of the neonatal septicaemia cases now are either LBW or preterm.[20]

Risk factors

Several obstetric and neonatal factors have been identified that may be associated with an increased risk of neonatal infection. In the present study, the most common neonatal risk factor responsible for the infection was prematurity 75 (36.58%), followed by respiratory distress 70 (34.15%). A study done by Stoll BJ et al indicated that 36% of 9,575 extremely low gestational age infants developed LONS; suggesting extreme prematurity is a risk factor of LONS.[21] Similar finding has been reported by Thakur S et al and Mhada TV et al.[15,22] The National Neonatal Perinatal Database (NNPD) reports of 2002-2003 identified respiratory distress as the commonest presentation of EONS.[3] We found respiratory distress in 70(34.15%) cases, whereas Bhat R et al reported it in (57.6%) cases.[23] In the present study, parenteral nutrition and mechanical ventilation were seen in 57 (27.80%) and 52 (25.36%) respectively. In Terhan EE et al study, they were the main risk factors for LONS.[24] Birth asphyxia is defined as APGAR score less than 7 at one minute of age.[3] We found birth asphyxia in 7 (3.36%) cases. Hayun M et al reported that apgar score <7 in the first minute have a risk of 14.05 times to the EONS occurrence.[25] Thakur S et al have reported it in 48% cases.[22] Birth asphyxia compromises the immunological profile of newborn. Both cellular and humoral immunity get suppressed in asphyxiated new-born baby. Also, the interventions like frequent suction, intubation, and prolonged ventilator care to manage the asphyxia may impart extra risk for acquiring infections in neonates. Maternal factors should also be considered as contributory risk factors for neonatal septicaemias. We found PROM in 65 (31.71%) and maternal pyrexia in 23 (11.22%) cases. Our findings were similar to study of Hayun M et al.[25]

Mode and place of delivery of neonatal septicaemia cases

In the present study, 105 (51.22%) neonates were delivered in hospital while 15 (07.31%) at home by normal vaginal delivery (Table 5). Our findings were in accordance with Manisha S et al who found higher infectivity rate in cases with normal delivery as compared to LSCS.[26] This indicates vertical transmission from maternal genital tract and therefore maternal risk factor should consider seriously. Contrary to them Gandhi S et al reported high incidence of sepsis in cases of babies born from caesarean section as compared to vaginal delivery.[13] Thakur S et al found that the difficult delivery (32%) in the form of caesarean, forceps or vacuum was much higher risk factor in their study.[22]

Bacteriological profile of neonatal septicaemia

The detection of microorganisms in a patient's blood has great diagnostic and prognostic significance, particularly, in neonates with suspected sepsis. Many infections in neonatal and paediatric age group can only be established on the basis of etiological agent recovered from blood. The causative organisms in neonatal sepsis vary from place to place and the frequency of the causative organisms is different in different hospitals and even in the same hospital at different time.

In the present study, gram-negative organisms predominated being responsible for 70.24% of cases of septicaemia. Similar findings were made by Muley VA et al and Tankhiwale et al.[18,27] The probable reasons being, new-borns most probably acquire these gram-negative rods from the vaginal and faecal flora of the mother and the environment where the delivery occurs.[28] The increased susceptibility of neonates to gram negative bacteria may be explained by the fact that antibodies against these organisms are primarily IgM type which do not transfer passively through placenta and are at very low level in blood at birth (about 5% of adult value) and reaches the adult level by 2 years of age. This is in contrast with IgG type, which are passively transferred to placenta and are almost at adult level at birth and falls gradually reaching lowest level around 3 to 4 months of age after which they start to rise again gradually. Adequate IgG levels at term (except IgG 2 subtype) afford protection against several gram-positive bacteria.[2]

In present study, the most frequently isolated organism was *Klebsiella pneumoniae* 54 (26.34%) followed by *S. aureus* 36 (17.56%). Our findings were similar to Muley VA et al.[18] *K. pneumoniae* was reported as a predominant pathogen in NNPD Report 2002-2003 and also by Sharma CM et al, Iregbu et al, Chelliah A et al and Tankhiwale SS et al.[3,11,27-29] *K.pneumoniae* and *S. aureus* can survive in the environment for a relatively long time and fairly widely distributed in the hospital environment and therefore have the potential for being transmitted from the environment to the patients through practices that breach infection control measures.[30]

The next common organism was *Pseudomonas aeruginosa* followed by *Escherichia coli* isolated in 27 (13.17%) and 23 (11.22%) respectively. Our result matches with Chelliah A et al[11] who reported *E. coli* in 7.2% and *P. aeruginosa* in 10% of the cases respectively.

The CONS, previously considered as a contaminant, has been recognized increasingly as a cause of bacteraemia. The ascendance of this group of staphylococci has created increased interpretative difficulties for the clinician, since the great majority of CONS isolates continue to represent contamination rather than true bacteraemia.[2] Our findings were comparable with Jyothi P et al, Chiliah A et al and Sharma CM et al who reported CONS in 27.5%, 10.9% and 4.38% cases respectively.[14,11,29]

The bacteriological profile differs in EONS and LONS and it also differs in developing and developed countries. In developed countries, gram-positive organism is predominant in both EONS and LONS whereas in developing countries gram negative organism is predominant in both EONS and LONS.[31] In the present study, gram negative bacilli were common aetiological agents as compared to gram positive cocci in both EONS and LONS. In EONS, the predominant isolate was *Klebsiella pneumoniae* 44 (32.12%), whereas in LONS the most common isolate was *S. aureus* 22 (32.35%) (Table 6).

In the present study, Gram negative bacilli showed maximum sensitivity to Imipenem and Amikacin and gram-positive cocci to Linezolide, Vancomycin and Amikacin. Similar antibiotic sensitivity pattern had been reported by Tankhiwale SS et al and Singh N et al.[27,32]

CRP test

Many studies have stressed the importance of CRP in neonatal septicaemia. CRP is considered as a "specific" but "late" marker of neonatal infection. If the CRP levels remain persistently normal, it correlates strongly with the absence of infection thereby guiding safe discontinuation of antibiotic therapy.[33] In contrast, elevated levels of CRP may be more difficult to interpret, especially for diagnosis of EONS because factors such as PROM, maternal fever, pregnancy-induced hypertension, prenatal steroid use, and fetal distress may also cause elevation of the CRP. Additionally, studies have suggested a physiologic variation of the CRP during the first few days. Studies also suggest that CRP is best used as part of a group of ancillary diagnostic tests to help determine if an infant has infection, rather than as a single test.[34] In the present study, out of 566 cases, CRP was positive in 244 (43.10%) cases (Table7). We found strong correlation of CRP and blood culture positivity. Out of total 205 culture positive cases 198 (96.59%) were CRP positive with a significant p value. Sensitivity and specificity of the CRP test was 96.59% and 87.26% respectively, suggesting that CRP testing may prove helpful marker to improve diagnostic accuracy in resource limited situations. Our findings were similar to Misra R et al.[35] In present study, CRP was positive in 46 (18.85%) cases even if culture negative. It may be because a variety of non-infectious conditions like meconium aspiration syndrome, traumatic or ischemic tissue injuries, hemolysis, or histologic chorioamnionitis may cause an elevation in the CRP levels.[33] CRP was negative in 07 (2.17%) of the culture positive cases. It may be because it takes 10-12 hours to change significantly after the onset of infection; the sensitivity of CRP is low during the early phase of sepsis.[33]

Mortality among septicaemia neonates

Mortality rate is higher in EONS compared to LONS[36]. In the present study, the difference between the mortality rate of EONS (25.54%) and LONS (19.11%) was not significant. (p=0.30603). Our result matches with the results of Movahedian et al.[36] The greater incidence of mortality in EONS may be due to lower host resistance, under weight babies, associated birth trauma and anoxia. The level of compliment in blood of newborn is less so also the immunoglobulins like IgM and IgG.[37] Further EONS is usually a fulminant and multisystemic infection; and hence has higher case fatality rate than late onset sepsis.[38]

CONCLUSION

Gram negative bacilli were found to be commonest cause of neonatal septicaemia in our setup. Male neonates were more prone to infection. Incidence of EONS was common as compared to LONS. Various neonatal and maternal risk factors were found to be associated with neonatal septicaemia. The prematurity and low birth weight neonates were at an increased risk of developing sepsis. Blood culture should be done in all suspected cases. The most common pathogen isolated in EONS cases was *K. pneumoniae* and in LONS cases was *S. aureus*. A good correlation between blood culture positivity and CRP was found in the present study. So, CRP testing may prove helpful marker to improve diagnostic accuracy in resource limited situations. Neonatal septicaemia is important cause of morbidity and mortality among the neonates. Early diagnosis, specific treatment and strict infection control practices in neonatal units can reduce neonatal mortality and morbidity.

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