



Bacterial Etiology of Neonatal Sepsis, Antibiotic Susceptibility Profile, and Associated Factors at Burdwan Medical College, Burdwan, West Bengal, India

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Abstract

Objective Neonatal sepsis remains to be a major cause of neonatal mortality and morbidity in developing countries like India. This study was aimed to identify the bacterial isolates and study antimicrobial profile among admitted babies with neonatal sepsis.

Methods A cross-sectional retrospective study was conducted in the sick neonatal wards and neonatal intensive care unit of Burdwan Medical College from March 2017 to February 2018. A total of 299 neonates suspected of neonatal sepsis was evaluated. Diagnosis of neonatal sepsis was made through positive blood culture. Positive samples were subcultured on specific media like blood, chocolate agar, nutrient, Muller–Hinton agar, and MacConkey plates, and the organisms were identified by gram staining and biochemical reactions. Antibiotic susceptibility was tested by Kirby–Bauer disc diffusion method.

Results Overall, 118 blood cultures out of 299 patients (39.46%) were bacteria-positive. Of these, 31.3% cases had early-onset septicemia (EOS), while 68.6% had late-onset septicemia (LOS). The prevalence of sepsis was higher in males (55.9%), preterm babies (58.47%), and low birth weight neonates (37.29%). The highest bacterial strains isolated were *Klebsiella spp.* (33.8%) followed by *Staphylococcus aureus* (25.8%), *Escherichia coli* (22.8%), coagulase-negative *Staphylococcus* (12.5%), *Pseudomonas spp.* (2.5%), *Enterococcus spp.* (1.6%), *Acinetobacter spp.* (0.8%), and *Burkholderia spp.* (0.8%). Resistance is high among the gram-negative bacteria, like *Enterobacter* and *Pseudomonas*, for piperacillin–tazobactam and cephalosporins but they are mostly sensitive to meropenem, colistin, and levofloxacin. Gram-positive bacteria, like *S. aureus*, are mostly resistant to amoxicillin–clavulanic acid but highly sensitive to linezolid, vancomycin, azithromycin, and teicoplanin.

Conclusion *K. spp.* and *S. aureus* are the most common isolates in our study. The level of resistance among the organisms toward conventional antibiotics like amoxicillin, cephalosporins, and piperacillin–tazobactam is alarmingly high. This warrants formulation of a hospital-specific guideline for antibiotic use and periodic review of the same.

Keywords

- ▶ bacterial sepsis
- ▶ antibiotic susceptibility
- ▶ early-onset sepsis
- ▶ late-onset sepsis
- ▶ neonates

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Introduction

Sepsis is one of the most common causes of neonatal deaths, globally. Prematurity, intrapartum-related complications, and birth defects are other causes of neonatal deaths worldwide.¹ Most infection-related deaths in the neonatal period occur in low-income and middle-income countries due to poor hygiene and suboptimal practices for infection control. A significant proportion of these deaths are caused by multidrug-resistant pathogens.² Despite the massive burden, few high quality data about neonatal sepsis are available from these countries.^{2,3} Such infection surveillance networks are a rarity in low-income and middle-income countries; the few available ones have used passive surveillance like the National Neonatal Perinatal Database (NNPD)³ and the Asia-Pacific Neonatal Infections Study (APNIS).⁴ Strengthening of locally owned information systems incorporating the causes of neonatal sepsis, particularly the responsible organisms and their antibiotic sensitivity patterns, can enable policy makers and program planners to use existing resources more effectively to achieve a better and effective goal.

In spite of great advances in antimicrobial therapy, neonatal life-support measures and the early assessment of risk factors, neonatal sepsis still continues to be a major cause for mortality and morbidity among neonates throughout the globe, mostly in the developing countries where reported rate of neonatal infection is 3 to 20 times higher than those reported in developed countries.⁵

According to onset of presentation, neonatal sepsis may be classified into (1) early-onset sepsis (EOS) that presents within the first 72 hours of life and (2) late-onset sepsis (LOS) that presents after 72 hours of age.⁶

The National Neonatology Forum's definition for probable sepsis is met when infant with clinical picture suggestive of sepsis with one or more of the following criteria⁷: (1) Existence of predisposing factors like maternal fever or foul-smelling liquor or prolonged rupture of membrane >12 hours or presence of gastric polymorphs >6/hpf; (2) positive sepsis screen, that is, two of the following four parameters, namely, total leucocyte count (TLC) < 5,000/cumm, band to total leukocytes ratio of >0.2, C-reactive protein (CRP) >1 mg/dL, and micro-erythrocyte sedimentation rate (ESR) >15 mm in first hour; and (3) radiological evidence of pneumonia.

Neonatal sepsis is a broad term incorporating neonatal septicemia, meningitis, pneumonia, arthritis, osteomyelitis, necrotizing enterocolitis, and urinary tract infections. It is a medical emergency and needs prompt treatment with proper antimicrobial therapy. Moreover, increased frequency of resistance to antimicrobials is a matter of serious concern.⁸⁻¹⁰

In the United States, since the 1980s, group B *Streptococcus* (GBS) has been the leading cause of EOS. Despite the implementation of intrapartum antibiotic prophylaxis against GBS, it remains the leading cause of EOS in term neonates. With the increased use of intrapartum antibiotic prophylaxis for GBS, gram-negative enteric bacteria have become the main cause of EOS in preterm infants. Enteric bacilli causing EOS include *Escherichia coli*, *Klebsiella spp.*,

Pseudomonas spp., *Haemophilus spp.*, and *Enterobacter spp.* Less-common organisms that can cause serious EOS include *Listeria* and *Citrobacter*. staphylococci and enterococci are more common in LOS.¹¹ In India, the spectrum of bacterial pathogens analyzed from hospital-based data collected by NNPD network from different centers is quite different from that of developed countries, *Klebsiella pneumoniae* was the commonest followed by *Staphylococcus aureus*, *E. coli*, and *P. spp.*³

Since etiological agents and their antimicrobial susceptibility pattern may vary region wise, as well as institution wise, knowledge of the prevalence of the local isolates and their antimicrobial sensitivity pattern is of importance to start early therapy. Our study aimed to study the prevalence of local isolates in babies with established neonatal sepsis admitted in both neonatal intensive care units (NICU) and sick neonatal care unit (SNCU), as well as define the antibiotic sensitivity pattern, so that we could formulate a rational antibiotic policy for both the units.

Materials and Methods

A hospital-based, cross-sectional, retrospective study was conducted among clinically suspected cases of neonatal sepsis admitted in SNCU and NICU during the time period of March 2017 to February 2018. The features that were suggestive of clinical sepsis included refusal to suck, hypothermia, hyperthermia, poor cry, lethargy, hypotonia, absence of neonatal reflexes, bradycardia, tachycardia, gasping respiration, apnea, respiratory distress, and abdominal distension.⁶ Those neonates having major congenital anomalies, acute bilirubin encephalopathy, grade-3 perinatal asphyxia, already started on antibiotics, hypoglycemia, suspected in-born errors of metabolism, and mother received antibiotics antenatally were excluded from the study. Overall, 299 neonates were chosen to be participants. The study was conducted after obtaining clearance from the ethical committee of the institution (memorandum no.: BMC-2962/ dated: December 1, 2016).

Clinical and demographic data were collected in a pre-designed set of questionnaires to be filled up by each parent at the time of admission. Gestational age, associated risk factors, place of referral, method of delivery, and birth weight were noted down. Blood of 2 mL was collected with intravenous (IV) cannula following strict aseptic precautions, before starting empirical antimicrobial treatment, of which 1 ml of blood was inoculated directly into pediatric aerobic blood culture bottle designed for BacT/Alert machine 3D 60 microbial system (BioMerieux, France) with maintaining proper asepsis, and remaining blood was utilized in sepsis screening.

All the samples were transported to the side laboratory without any delay. Blood culture bottles were sent to the bacteriology laboratory of the Department of Microbiology for processing. Blood culture were followed up for 7 days, those bottles flagged positive were subcultured in MacConkey agar media, blood agar, and chocolate agar media. Bacteria are isolated and identified based on gram stain, colony morphology, and biochemical test. Antimicrobial

Table 1 General characteristics and clinical profile of neonates with established sepsis

Variables	Total (n = 118) n (%)	Early-onset sepsis (n = 37) n (%)	Late-onset sepsis (n = 81) n (%)	p-Value
Gender				
Males	66 (55.93)	20 (54.05)	46 (56.79)	0.781
Females	52 (44.07)	17 (45.95)	66 (55.93)	
Gestational age (wk)				
Preterm	69 (58.47)	9 (24.32)	60 (58.47)	<0.001 ^a
Term	44 (37.29)	23 (62.16)	21 (25.93)	<0.001 ^a
Postterm	5 (4.24)	5 (13.51)	0 (0)	0.016 ^a
Birth weight (kg)				
< 1	11 (9.32)	0 (0)	11 (9.32)	0.000 ^a
1–1.5	28 (23.73)	5 (13.51)	23 (23.73)	0.048 ^a
1.5–2	44 (37.29)	14 (37.84)	30 (37.04)	0.943
> 2.5	35 (29.66)	18 (48.65)	17 (20.99)	0.003 ^a
Mode of delivery				
Vaginal	65 (55.08)	19 (51.35)	46 (56.79)	0.582
Caesarean	53 (44.92)	18 (48.65)	35 (43.21)	
Outcome				
Mortality	15 (12.71)	7 (18.92)	8 (9.88)	0.171

^aStatistically significant.

sensitivity was done by the modified Kirby–Bauer disc diffusion method following Clinical and Laboratory Standards Institute guideline.¹²

Two to three colonies of the isolated organisms were mixed with normal saline and turbidity of the mixture was made equivalent to 0.5 MacFarland and was swabbed over Muller-Hinton agar plates. Within 15 minutes, antibiotic discs (HiMedia, India) were placed with desired amounts of antibiotics and the plates were incubated overnight at 37°C. Following antibiotic, disc was used for susceptibility testing of isolates: cotrimoxazole (25 µg), amoxicillin/clavulanic acid (20/10 µg), piperacillin/tazobactam (100/10 µg), cefotaxime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg), meropenem (10 µg), imipenem (10 µg), and azithromycin (30 µg); aminoglycosides, such as amikacin (30 µg) and gentamicin (10 µg); fluoroquinolones, such as ciprofloxacin (5 µg) and levofloxacin (5 µg); and linezolid (30 µg) and clindamycin (2 µg). Minimum inhibitor concentration (MIC) of teicoplanin (10 µg), vancomycin (30 µg), and colistin (10 µg) was determined by the Epsilon meter test (E test).

Statistical Analysis

All data were put in Microsoft excel. SPSS version 20.0 (Statistical Packages for Social Sciences Inc. Chicago, Illinois, United States) was used for data analysis. Categorical variables were expressed in percentage and frequencies and compared across the groups using Pearson's Chi-square test for independence of attributes and Fisher's exact test for appropriate. An α level of 5% has been taken, that is, if any *p*-value was less than 0.05, it was considered to be statistically significant.

Results

General Characteristics and Clinical Profile

Among these 299 clinically suspected cases of neonatal sepsis, blood culture was positive in 118 cases (39.46%) while 181 samples were culture negative (►Table 1).

Among the culture-positive cases, 66 (55.93%) of the neonates were males, while 52 (44.07%) were females at a ratio of 1.27:1. The distribution of neonates according to gestational age shows the following: preterm, 58.47%; term, 37.29%; and postterm, 4.24%. The distribution of neonates according to birth weight was as follows: extremely low birth weight (ELBW), 9.32%; very low birth weight (VLBW), 23.73%; low birth weight (LBW), 37.29%; and normal weight, 29.66%. Of these, 55.08% neonates were born by vaginal delivery, while 44.92% by caesarean section.

Bacteriological Profile

Distribution of blood culture isolates showed 46 (38.3%) were gram-positive bacteria and 74 (61.6%) were gram-negative bacteria as shown in ►Table 2. The highest bacterial strains isolated were *K. spp.* (33.8%) followed by *S. aureus* (25.8%), *E. coli* (22.8%), coagulase-negative *Staphylococcus* (CoNS; 12.5%), *P. spp.* (2.5%), *E. spp.* (1.6%), *Acinetobacter spp.* (0.8%), and *Burkholderia spp.* (0.8%).

The maximum number of bacterial strains isolated in EOS was *E. coli* (37.8%) followed by *K. spp.* (29.7%). However, the highest bacterial strains in LOS were *K. spp.* (34.94%) followed by *S. aureus* (28.9%), as shown in ►Table 3.

Table 2 Bacteriological profile: frequency of isolates in culture positive sepsis

Organism	No of isolates (n = 120)	Proportion (%)
Gram-negative organisms		
<i>Klebsiella spp.</i>	40	33.89
<i>Escherichia coli</i>	27	22.88
<i>Pseudomonas spp.</i>	3	2.50
<i>Enterobacter spp.</i>	2	1.66
<i>Acinetobacter spp.</i>	1	0.83
<i>Burkholderia spp.</i>	1	0.83
Gram-positive organisms		
<i>Staphylococcus aureus</i>	31	25.83
CoNS	15	12.50
Total	120	100

Abbreviation: CoNS, coagulase-negative *Staphylococcus*.

Of these 118 patients, a total of 120 bacterial isolates were cultured with two patients having two isolated bacteria from their blood cultures, while two patients had bacteria along with isolated fungus (*Candida albicans*) shown in (►Table 4).

Antibiotic Susceptibility Pattern Gram-Negative Bacteria

K. spp. showed the maximum sensitivity to levofloxacin (97%), amikacin (89%), and meropenem (69%) and low sensitivity to amoxicillin–clavulanic acid, cephalosporins, and piperacillin–tazobactam. *K. spp.* was highly sensitive to colistin (100%).

E. coli had 100% sensitivity to meropenem, cotrimoxazole, and colistin; 96% sensitivity to amikacin and 80% to levofloxacin, while showed low sensitivity to antibiotics like amoxicillin, cephalosporins, and piperacillin–tazobactam.

A. spp. was highly sensitive to colistin and ceftazidime (100%) but showed 100% resistance to rest antibiotics like gentamicin, amikacin, ciprofloxacin, levofloxacin, and cephalosporins.

P. spp. had 100% sensitivity to ceftazidime, levofloxacin, and meropenem and 50% sensitivity to amikacin, as well as 100% resistance to gentamicin and all β -lactam antibiotics.

E. spp. showed 100% sensitivity to levofloxacin and ciprofloxacin and 100% resistance to cotrimoxazole, amikacin, gentamicin, and ceftriaxone.

B. spp. showed 100% sensitivity to ceftazidime, meropenem, and cotrimoxazole and 67% sensitivity, as well as 100% resistance, to amikacin and gentamicin.

Gram-Positive Bacteria

CoNS was 100% sensitive to clindamycin and levofloxacin, 100% sensitive to vancomycin, 83% to amikacin, 80% to

Table 3 Bacteriological profile: frequency of isolates in early-onset and late-onset sepsis

Organism	EOS (n = 37) n (%)	LOS (n = 83) n (%)	p-Value
Gram-negative organisms			
<i>Escherichia coli</i>	14 (37.84)	13 (15.66)	0.013 ^a
<i>Klebsiella spp.</i>	11 (29.73)	29 (34.94)	0.569
<i>Enterobacter spp.</i>	1 (2.7)	1 (1.2)	0.608
<i>Pseudomonas spp.</i>	0 (0)	3 (3.61)	0.078
<i>Acinetobacter spp.</i>	0 (0)	1 (0.83)	0.314
<i>Burkholderia spp.</i>	0 (0)	1 (0.83)	0.314
Gram-positive organisms			
<i>Staphylococcus aureus</i>	7 (18.92)	24 (28.92)	0.219
CoNS	4 (10.81)	11 (13.25)	0.699

Abbreviation: CoNS, coagulase-negative *Staphylococcus*.

^aStatistically significant.

Table 4 Types of isolates

Isolates	Type	No. of patients (n = 118)	Percentage
Single isolated organism	Gram positive	44	37.28
	Gram negative	70	59.32
Two isolated organisms	Gram positive + gram negative	1	0.84
	Gram negative + gram negative	1	0.84
	Gram negative + <i>Candida albicans</i>	2	1.69

Table 5 Showing antibiotic susceptibility pattern of bacterial isolates (S/T %)

Antibiotic	<i>Klebsiella</i> n (%)	<i>S. aureus</i> n (%)	<i>E. coli</i> n (%)	CoNs n (%)	<i>Pseudomonas</i> n (%)	<i>Acinetobacter</i> n (%)	<i>Burkholderia</i> n (%)	<i>Enterobacter</i> n (%)
Amoxicillin/clavulanat	4/14 (28)	12/31 (39)	0/5 (0)	3/10 (30)	0/2 (0)			
Ceftriaxone	7/39 (18)	8/24 (33)	10/25 (40)	3/7 (43)	0/3 (0)	0/1 (0)		0/2 (0)
Cefotaxime	0/27 (0)	0/5 (0)	10/25 (40)			0/1 (0)		
Cefuroxime	2/14 (14)	7/31 (23)	7/31 (33)	6/15 (40)				
Ceftazidime	16/39 (41)	0/4 (0)	6/26 (23)	2/6 (33)	3/3 (100)	1/1 (100)	1/1 (100)	
Amikacin	35/39 (89)	26/31 (84)	25/26 (96)	10/12 (83)	1/2 (50)	0/1 (0)	0/1 (0)	0/2 (0)
Gentamicin	27/39 (69)	20/31 (64)	17/24 (71)	6/15 (40)	0/3 (0)	0/1 (0)	0/1 (0)	0/2 (0)
Linezolid		21/21 (100)	0/2 (0)	11/15 (73)	0/2 (0)			0/2 (0)
Cotrimoxazole	7/14 (50)	16/24 (67)	8/8 (100)	0/3 (0)				0/2 (0)
Imipenem	6/13 (46)	26/26 (100)	0/3 (0)	4/16 (50)				
Meropenem	18/26 (69)	20/20 (100)	10/10 (100)	0/2 (0)	3/3 (100)		1/1 (100)	2/2 (100)
Levofloxacin	38/39 (97)	16/24 (67)	16/20 (80)	7/7 (100)	3/3 (100)	0/1 (0)		2/2 (100)
Azithromycin		23/31 (74%)		12/15 (80)				
Ciprofloxacin	29/39 (74)	13/31 (42)	15/26 (58)	5/15 (33)	2/2 (100)	0/1 (0)		2/2 (100)
Pipzo	12/39 (30)	12/27 (44)	2/12 (17)	4/12 (33)				
Teicoplanin		10/10 (100)		4/10 (40)		0/1 (0)		0/2 (0)
Vancomycin		31/31 (100)		14/14 (100)				
Colistin	7/7 (100)		10/10 (100)			1/1 (100)	0/1 (0)	

Abbreviations: *E. coli*, *Escherichia coli*; Pipzo, piperacillin-tazobactam; *S. aureus*, *Staphylococcus aureus*; S/T, no. of sensitive organisms/total.

azithromycin, and 73% to linezolid, as well as less sensitive to imipenem, ciprofloxacin, amoxicillin + clavulanic acid and cephalosporins.

S. aureus showed 100% sensitivity to vancomycin, linezolid, teicoplanin, meropenem, and imipenem and 84% to amikacin and 74% to azithromycin, as well as low sensitivity to piperacillin–tazobactam, gentamicin, ciprofloxacin, levofloxacin, cotrimoxazole, cephalosporins, and amoxicillin/clavulanate (► Table 5).

Discussion

Blood culture was positive in 118 cases, that is, 39.46% among 299 clinically suspected sepsis cases. The study shows culture-positive sepsis was much higher in male neonates (55.93%) compared to female neonates (44.07%). Different authors have documented that male babies are more susceptible to neonatal sepsis than female babies.^{13,14} The high predilection of male babies for neonatal sepsis may be due to the fact that X-chromosome is potentially more immune in comparison to Y-chromosome because of X-linked immune-regulatory genes.¹⁴

In this study, the occurrence of sepsis was much higher in preterm babies (58.47%) in comparison to term and postterm babies. Different authors also documented higher incidence of sepsis in preterm babies and it was also directly related to the degree of prematurity,^{15,16} as the preterm neonates had greater compromise in their immune system. The present study is well correlated with the observation by different authors.

Out of total cases, ELBW babies were 11 (9.32%), VLBW babies were 28 (23.73%), LBW babies were 44 (37.29%), and normal birth weight babies were 35 (29.66%). The highest incidence of culture-positive sepsis was seen among LBW babies followed by normal birth weight babies. Different authors documented that LBW babies were more susceptible to develop sepsis because of their deficiency in the development of immune system along with poor transplacental acquisition of maternal immunoglobulin.¹⁷ Similar observation was also noted by Singh.¹⁰

K. spp. was the commonest organism causing neonatal sepsis (33.89%) followed by *S. aureus* (25.83%). These findings are similar with the NNPD 2002 to 2003 reports³ and a study conducted by Jyothi et al in South India where the incidence of *K. spp.* is the highest.¹⁸ Roy et al, in a study in tertiary care hospital in northern India, have documented *K. spp.* as the predominant organism.¹⁹

LOS has been found to be mostly caused by *K. spp.* (34.94%) followed by *S. aureus* (28.92%) in this study. Studies by Verma et al in the Western part of India and Panigrahi et al in the Eastern India have also obtained similar results.^{20,21}

E. coli (37.84%) followed by *K. spp.* (29.73%) are the commonly isolated pathogens from babies in EOS. Studies by Mendoza-Palomar et al and Stoll et al have reported that *E. coli* as an important cause of EOS.^{22,23}

GBS is a leading cause of neonatal sepsis in developed countries but it was not isolated from our study participants.

A study by Simonsen et al has reported incidence of GBS in EOS but according to Kuruvilla et al and Viswanathan et al, GBS is rarely documented in India.^{24–26}

Other organisms isolated in this study were CoNS, *Pseudomonas*, *B. spp.*, *Acinetobacter*, and *Enterobacter*.

CoNS, as an emerging pathogen in neonatal sepsis cases, has been reported by Marchant et al.²⁷ Sepsis due to CoNS, *Pseudomonas*, and *Acinetobacter* have been documented in the NNPD 2002 to 2003 reports.³

Our study concluded that gram-negative *Enterobacteriaceae* (*Klebsiella* and *E. coli*) was mostly sensitive to meropenem, amikacin, colistin, and levofloxacin but resistant to cephalosporins and piperacillin–tazobactam. *Enterobacter* was resistance to most of the antibiotics except fluoroquinolones. *Pseudomonas* was found to be sensitive to ceftazidime, levofloxacin, meropenem, and cotrimoxazole mainly. *Acinetobacter* was found to be only sensitive to ceftazidime and colistin, while *Burkholderia* was found to be sensitive to ceftazidime, meropenem, and cotrimoxazole.

On the other hand, the gram-positive isolates (*S. aureus*) were mostly sensitive to amikacin, azithromycin, linezolid, and vancomycin but resistant to amoxicillin–clavulanic acid and cephalosporins. Studies by Sheth et al in the Western part of India and Viswanathan et al in the Eastern India have also found high proportion of resistance to the common first line antibiotics.^{28,29} CoNS was mostly sensitive to fluoroquinolones, clindamycin, azithromycin, colistin, linezolid, amikacin, and vancomycin. Almost similar type of result had been revealed from other places in India.^{19,30,31}

Limitations of this Study

This is a hospital-based study involving small number of study samples. So, the results of this study may not be applied to the others hospital or community. For this, large scale multicentric study is needed. Inability to identify the anaerobes was another limitation of the study.

Conclusion

This helps us conclude that empirically chosen first line antibiotics, like ampicillin, piperacillin–tazobactam, and cephalosporins, are mostly ineffective when neonatal sepsis is suspected in our unit.

Differences of antibiotic sensitivity and resistance pattern among various studies can be explained by the regional variation of prevalent organisms and different antibiotic regimens used for treating those organisms.^{32,33}

Neonatal mortality among the patients has been reported to be 12.71% which is similar to findings conducted by the Delhi Neonatal Infection Study (DeNIS) study.³⁴

Recommendations

There is need to develop an antibiotic policy tailored to the type of antibiotic resistance documented in any hospital and update that at least every 2 years.

Authors' Contributions

T.D.: data collection, conception, and designing of study; J. S.: analysis and interpretation of data and preparing manuscript; K.P.: microbiological laboratory work; K.L. B.: planning of study, treating physician, and critical revision of article. All authors reviewed and approved the final version of the manuscript for submission.

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Conflict of Interest

None declared.

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