

# SPECIES DISTRIBUTION AND ANTIMICROBIAL SENSITIVITY PATTERN OF ETIOLOGIC AGENTS IN PATIENTS WITH NEONATAL SEPSIS, NATIONAL CHILDREN'S HOSPITAL, HA NOI, VIETNAM, 2019–2021



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**Abstract.** Neonatal sepsis is one of the significant causes of morbidity and mortality in neonates, especially in developing countries. This study investigates the species distribution and antimicrobial susceptibility pattern of agents causing neonatal sepsis in a northern hospital in Vietnam. *Materials and methods.* All in-term neonates treated at the Neonatal Center, National Children's Hospital, Vietnam between December 2019, and April 2021 who met the clinical criteria for sepsis and positive blood cultures were enrolled. Species identification and antimicrobial susceptibility testing were performed with Vitek 2 Compact (bioMerieux, France). *Results.* Eighty-five neonates were included with the majority of cases being early-onset sepsis (61.2%, 95% CI: 50.6–71.8%). Gram-negative, Gram-positive, and fungal isolates constituted 50.6%, 40%, and 9.4%, respectively. The most common agent was *Staphylococcus aureus* (28.2%) followed by *Klebsiella pneumoniae* and *Escherichia coli* (16.5% each). For those with bacteriological sepsis, Gram-negative pathogens were predominant in early-onset sepsis whereas Gram-positive pathogens were predominant in late-onset sepsis (75.0% (33/44) vs 69.7% (23/33),  $p < 0.001$ ). Antibiotic resistance was common among bacterial isolates, but antifungal resistance was not detected among isolates of *Candida* sp. Vancomycin and fluoroquinolone were very effective against Gram-positive organisms while piperacillin + tazobactam, aztreonam, and ertapenem were potent drugs against Gram-negative organisms. *Conclusion.* Routine investigation of microbial profiles and antimicrobial susceptibility patterns is essential to guiding strategies for the choices of empirical antimicrobials.

**Key words:** neonatal sepsis, species, antimicrobial susceptibility, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli*.

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## ВИДОВОЕ РАСПРЕДЕЛЕНИЕ И ХАРАКТЕРИСТИКА АНТИМИКРОБНОЙ ЧУВСТВИТЕЛЬНОСТИ ЭТИОЛОГИЧЕСКИХ АГЕНТОВ У ПАЦИЕНТОВ С СЕПСИСОМ НОВОРОЖДЕННЫХ ПО ДАННЫМ НАЦИОНАЛЬНОЙ ДЕТСКОЙ БОЛЬНИЦЫ (ХАНОЙ, ВЬЕТНАМ) ЗА ПЕРИОД 2019–2021 гг.

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**Резюме.** Неонатальный сепсис является одной из основных причин заболеваемости и смертности новорожденных, особенно в развивающихся странах. Настоящее исследование было направлено на изучение видового распределения бактерий, вызывающих неонатальный сепсис, и профиля их чувствительности к противомикробным препаратам в больнице на севере Вьетнама. *Материалы и методы.* В исследование были включены все доношенные новорожденные, проходившие лечение в неонатальном центре Национальной детской больницы Вьетнама в период с декабря 2019 г. по апрель 2021 г., которые соответствовали клиническим критериям сепсиса и у которых был получен положительный результат посева крови. Идентификацию видов возбудителей и определение чувствительности к противомикробным препаратам проводили с помощью бактериологического анализатора «Vitek 2 Compact» (bioMérieux, Франция). *Результаты.* В исследовании приняли участие 85 новорожденных, у большинства из которых отмечен сепсис с ранним началом (61,2%, 95% ДИ: 50,6–71,87%). Грамотрицательные, грамположительные и грибковые изоляты составляли 50,6, 40 и 9,4% соответственно. Наиболее частым возбудителем был *Staphylococcus aureus* (28,2%), за ним следовали *Klebsiella pneumoniae* и *Escherichia coli* (по 16,5%). У больных с бактериальным сепсисом грамотрицательные возбудители преобладали при сепсисе с ранним началом, тогда как грамположительные возбудители — при сепсисе с поздним началом (75,0% (33/44) против 69,7% (23/33),  $p < 0,001$ ). У бактериальных изолятов часто выявлялась устойчивость к антибиотикам, тогда как у изолятов *Candida* spp. резистентности к противогрибковым препаратам установлено не было. Ванкомицин и фторхинолон были крайне эффективны в отношении грамположительных микроорганизмов, в то время как пиперациллин + тазобактам, азтреонам и эртапенем проявляли выраженную активность против грамотрицательных микроорганизмов. *Выводы.* Рутинное исследование микробных профилей и моделей чувствительности к противомикробным препаратам имеет важное значение для определения стратегии выбора эмпирических противомикробных препаратов.

**Ключевые слова:** неонатальный сепсис, виды, антимикробная чувствительность, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Escherichia coli*.

## Introduction

Neonatal sepsis is one of the significant causes of morbidity and mortality in neonates, especially in developing countries. Globally, neonatal sepsis is estimated to cause from 1.3 to 3.9 million cases and between 400 000 and 700 000 deaths annually [41]. The mortality rate for neonatal sepsis is between 1% and 5% for sepsis and 9% to 20% for severe sepsis [14]. Furthermore, the rate of mortality is not equal and far higher in developing countries (roughly ~34/1000 live births) compared to that in developed countries (~5/1000) [4]. One of the main challenges to the effective management of neonatal sepsis is the occurrence of antimicrobial resistance among clinically relevant pathogens [45]. For this reason, an antimicrobial regime to treat causative agents is ideally based on the results of blood culture and drug sensitivity tests [32]. However, these results are available only for cases with positive blood cultures, the technique that is considered the gold standard for diagnosis but lacks sensitivity and cannot produce results quickly [34]. So early initiation of empiric antimicrobial therapy

based on updated data on the local profile of species distribution and antimicrobial resistance of causative pathogens is very important [18, 24]. In addition, this approach could reduce the inappropriate use of antibiotics, and consequently, reduce the emergence of antimicrobial-resistant pathogens [5].

Vietnam is a developing country and infection is still the leading primary cause of hospital admission and mortality in neonates [37]. Geographically, Vietnam is divided into northern, central, and southern regions. There have been some reports of causative microorganisms of neonatal sepsis from the central and south of Vietnam, but data from northern Vietnam is limited [35, 36]. We conducted this study to investigate the species distribution and antimicrobial susceptibility pattern of agents causing neonatal sepsis in a northern hospital in Vietnam.

## Materials and methods

*Ethical consideration.* This retrospective study is part of thesis work for the fulfillment of Doctor of Philosophy in Health Studies and obtained clearance

from the ethics committee of the Vietnam National Institute of Malaria, Parasitology and Entomology (NIMPE). Written or verbal consent was obtained from all the legal representatives of the patients.

This study was carried out at the Neonatal Centre, National Children's Hospital, Vietnam between December 2019, and April 2021. Agent isolation and analysis were done in the laboratories of the Department of Microbiology, National Children's Hospital.

**Data collection.** All in-term newborns (0–28 days of age) visiting the Centre with clinical symptoms/signs that met the criteria for sepsis and positive results of blood culture were enrolled in the study. Patients receiving blood or having severe congenital diseases that affect vital function were excluded from the study. Demographic and clinical findings were obtained from electronic medical records using a standardized case report form.

**Microorganism analysis.** To isolate the responsible agents for sepsis, 2 ml of blood were collected from two different sites and subjected to culture in two bottles, one for aerobic bacteria and one for anaerobic bacteria or fungi according to the adjustment of responsible clinicians. Species identification and antimicrobial susceptibility testing (AST) were performed with “Vitek 2 Compact” (using VITEK® 2 GN ID, VITEK® 2 GP ID and VITEK® 2 YST ID cards for identification of Gram-negative, Gram-positive isolates and yeast respectively, AST GN 86, AST GP 67 and AST-YS08 GN cards for AST of GN, GP and yeast respectively, bioMérieux, France) following the manufacturer's instructions.

**Definition.** The diagnosis of neonatal sepsis in the present study was based on criteria issued by European Medicines Agency [12]. An infection presented between birth and 72 hours of life was classified as early-onset sepsis (EOS) and “late-onset sepsis” (LOS) was sepsis that occurs after 72 hours of life. The minimum inhibition concentration (MICs) was categorised as S (susceptible) and R (resistant) according to species-specific breakpoints established by the Clinical and Laboratory Standards Institute [6, 7, 8].

**Statistics.** Data were analyzed using SPSS software version 20.0. Categorical data were described by case number (n) and percentages. Continuous data were expressed as mean±standard deviation (SD). Categorical variables were compared by Chi-square test and the accepted level of significance was two-tailed  $p < 0.05$ .

## Results

During the study period, 85 in-term neonates met the included criteria and were enrolled. The male-to-female patient ratio was 1.2:1 and the mean age of gestation was 38.6 weeks. About one-quarter of neonates had low birth weight but none had very low birth weight ( $< 1.5$  kg). More than half of them

**Table 1. Baseline characteristics of 85 patients recruited with neonatal sepsis**

Variable	% (CI 95%) or mean±SD	
<b>Demographic features</b>		
Gender	Male	54.1 (43.3–64.9)
	Female	45.9 (35.1–56.7)
Age (days)	10.4±8.2	
Birth weight (grams)	2918.2±548	
Low birth weight ( $\leq 2500$ g)	25.9 (16.4–23.2)	
Gestation age (weeks)	38.6±1.1	
Onset of sepsis	EOS	61.2 (50.6–71.8)
	LOS	38.8 (28.3–49.4)
<b>Maternal features</b>		
Mode of delivery*	SVD	50.6 (39.7–61.4)
	CS	49.4 (38.6–60.3)
History of infection during the gestation period#	15.3 (7.5–23.10)	

**Note.** \*CS Cesarean Section, SVD Spontaneous Vaginal Delivery. #Mothers with history of infection included 8 with genital infection, 7 with bronchitis, gingivitis, or urinary tract infections, and 2 with chorioamnionitis.

were delivered by SVD and about one-fifth of the neonates' mothers had a history of infection during the gestational period. The majority of cases were defined as EOS (61.2%) (Table 1).

There were 85 microbial isolates belonging to 19 different kinds of organisms. Bacteria composed the most (90.6%) while fungi accounted for only 9.4% of the isolates. For those with bacteriological sepsis, Gram-negative (GN) isolates were more common than Gram-positive (GP) isolates (55.8% and 44.2% respectively). In all groups, the most predominant agent was *S. aureus* (28.2%) while *K. pneumoniae* and *E. coli* (16.5% each) were the predominant causative agents in GN bacteria. Gram-negative pathogens were predominant in EOS whereas GP pathogens were predominant in LOS [75.0% (33/44) vs 69.7% (23/33),  $p < 0.001$ ]. There were 5 species of fungi recovered and *C. albicans* was the most prevalent agent (50%, 4/8). All cases with candidemia were classified as EOS (Table 2).

Gram-positive isolates were associated with minimal sensitivity to clindamycin (13.0%), oxacillin (14.3%), and benzyl penicillin (17.9%). Of note, 90.0–95.2% of GP bacteria were sensitive to fluoroquinolone and 100% of isolates were sensitive to vancomycin. *S. aureus* (the most common pathogen isolated) showed high sensitivity to vancomycin, fluoroquinolones (100%), and gentamicin (83.3%) (Table 3).

Gram-negative isolates demonstrated a low sensitivity to cefotaxime (8.3%), ampicillin + sulbactam (9.5%), ceftazidime (45.8%), and cefoxitin (50.0%), moderate sensitivity to ciprofloxacin (60%), moxifloxacin (69.2%), tobramycin (63.2%), ceftriaxone (63.6%), amikacin (68.6%), and imipenem (72.7%). The drugs that show high efficacy against GN organisms was piperacillin + tazobactam (sensitivity

**Table 2. Distribution of bloodstream infection isolates**

Groups	Species	EOS	LOS	Total	%
Gram-negative	<i>Klebsiella pneumoniae</i>	12	2	14	16.5
	<i>Escherichia coli</i>	7	7	14	16.5
	<i>Serratia marcescens</i>	4	0	4	4.7
	<i>Acinetobacter baumannii</i>	3	0	3	3.5
	<i>Burkholderia cepacia</i>	2	1	3	3.5
	<i>Pseudomonas aeruginosa</i>	2	0	2	2.4
	<i>Enterobacter cloacae</i> complex	1	0	1	1.2
	<i>Stenotrophomonas maltophilia</i>	1	0	1	1.2
	<i>Elizabethkingia meningoseptica</i>	1	0	1	1.2
	Subtotal	33	10	43	50.6
Gram-positive	<i>Staphylococcus aureus</i>	5	19	24	28.2
	GBS*	3	4	7	8.2
	<i>Listeria monocytogenes</i>	1	0	1	1.2
	<i>Enterococcus faecium</i>	1	0	1	1.2
	<i>Bacillus cereus</i>	1	0	1	1.2
	Subtotal	11	23	34	40.0
Fungi	<i>Candida albicans</i>	4	0	4	4.7
	<i>Candida tropicalis</i>	1	0	1	1.2
	<i>Candida krusei</i>	1	0	1	1.2
	<i>Candida parapsilosis</i>	1	0	1	1.2
	<i>Candida guilliermondii</i>	1	0	1	1.2
	Subtotal	8	0	8	9.4
	Total	52	33	85	100

Note. \*GBS: Group B streptococcus.

**Table 3. Profile of antimicrobial sensitivity among Gram-positive isolates\***

Groups	Antibiotics	<i>S. aureus</i>	GBS	Other	Total	%
Aminoglycosides	Amikacin		1/2	0/1	1/3	33.3
	Gentamycin	15/18	0/1		15/19	78.9
Beta-lactam	Benzyl penicillin	0/22	5/6		5/28	17.9
	Oxacillin	0/23	4/4	0/1	4/28	14.3
	Ticarcillin		0/1		0/1	0.0
	Cefazolin		0/1		0/1	0.0
	Cefoxitin		0/1		0/1	0.0
	Ceftriaxon		2/3	0/1	2/4	50.0
	Cefoperazone		0/1		0/1	0.0
	Ceftazidim		0/1		0/1	0.0
	Cefotaxim		2/3		2/3	66.7
	Cefepime		0/1	0/1	0/2	0.0
	PiTa <sup>#</sup>	1/1	1/2	0/1	2/4	50.0
	AmS <sup>**</sup>	1/1	2/4	1/2	4/7	57.1
	Aztreonam		0/1		0/1	0.0
	Ertapenem		0/1	0/1	0/2	0.0
	Meropenem	2/2	0/1		2/3	66.7
Imipenem		0/1	1/1	1/2	50.0	
Fluoroquinolone	Ciprofloxacin	17/17	0/1	1/2	18/20	90.0
	Moxifloxacin	15/15	5/5	0/1	20/21	95.2
	Levofloxacin	20/20	5/6	0/1	25/27	92.6
Glycopeptide	Vancomycin	24/24	7/7	2/2	33/33	100
Lincosamide	Clindamycin	1/16	2/7		3/23	13.0

Notes. \*N = number of sensitive isolates/Number of tested isolates. #PiTa: Piperacillin + tazobactam. \*\*AmS: Ampicillin + sulbactam.

**Table 4. Profile of antimicrobial sensitivity among Gram-negative isolates\***

Groups	Antibiotics	<i>K. pneumoniae</i>	<i>E. coli</i>	Other	Total	%
Aminoglycosides	Amikacin	8/14	12/13	4/8	24/35	68.6
	Gentamycin	3/11	7/13	4/6 6/10	16/34	47.1
	Tobramycin	4/8	4/6	4/5	12/19	63.2
Beta-lactam	Cefazolin		1/1	0/1	1/2	50.0
	Cefoxitin	3/8	5/9	2/3	10/20	50.0
	Ceftriaxon	4/8	6/9	4/5	14/22	63.6
	Cefoperazone	1/1			1/1	100.0
	Ceftazidim	5/11	4/6	2/7	11/24	45.8
	Cefotaxim	0/6	0/2	1/4	1/12	8.3
	Cefepime	2/2	4/4	1/2	7/8	87.5
	PiTa <sup>#</sup>	5/5	3/3	2/3	10/11	90.9
	AmS <sup>**</sup>	0/9	2/11	0/1	2/21	9.5
	Aztreonam	5/5	4/5	3/3	12/13	92.3
	Ertapenem	6/6	4/5	3/3	13/14	92.9
	Meropenem	3/4	3/6	4/6	10/16	62.5
Imipenem	6/8	8/11	2/3	16/22	72.7	
Fluoroquinolone	Ciprofloxacin	5/8	3/7	7/10	15/25	60.0
	Moxifloxacin	4/8	2/4	3/5	9/13	69.2
	Levofloxacin	4/8	4/8	10/13	18/29	62.1

**Notes.** \*N = number of sensitive isolates/Number of tested isolates. #PiTa: Piperacillin + tazobactam. \*\*AmS: Ampicillin + sulbactam.

rate of 90.9%), aztreonam (92.3%), and ertapenem (92.9%) (Table 4).

Resistance to tested antifungals (caspofungin, fluconazole, micafungin, voriconazole, fluorocytosine, amphotericin B) was not detected among isolates of *Candida* spp.

## Discussion

There were 85 in-term neonates involved in this study. The characteristics of our patients were comparable to those in some other studies in Vietnam reporting the predominance of males, and EOS among patients with neonatal sepsis [35, 36, 37].

The predominance of bacteria as the causative agent of neonatal sepsis (90.6%) in our study is in line with many previous reports [23, 29, 44]. The majority of GN isolates among patients with bacteriological sepsis is identical to those previously reported in India [29], Myanmar [28] and Vietnam [23]. Similarly, the majority of GN organisms among EOS and GP bacteria among LOS patients in our patients are concordant with those in the literature [3, 46]. A very high prevalence of GN organisms among EOS sepsis (90.4%) has been reported in Indonesia [31].

Considering single species, the leading cause of neonatal sepsis was *S. aureus* (28.2%), followed by *K. pneumoniae* and *E. coli*. Our results seem to replicate previous data demonstrating the predominance of *S. aureus*, *K. pneumoniae* and *E. coli* as the causative agents of neonatal sepsis in developing countries [15, 40]. Surprisingly, the prevalence of *S. aureus* in our study was high which diverges from the very low rates (4–4.5%) reported in central and south-

ern Vietnam [35, 37]. However, our result conforms with those reported in Ethiopia [16], and India [22]. In our opinion, this difference could reflect the geographic variation of agents causing neonatal sepsis and emphasize the importance of routine investigation of the distribution species to get updated profiles of aetiologic organisms in different regions [38]. Of the GN organisms, *K. pneumoniae*, *E. coli* were the most common isolates (16.5%) which was in accordance with other findings in Vietnam [23, 35]. The rate of sepsis caused by GBS in our study (8.2%, 7/85) was lower than that in developed countries (43–58%) [46]. This minority may be the consequence of the low prevalence of GBS colonization among pregnant women in Vietnam [11, 17]. In the literature, the incidence of neonatal sepsis caused by GBS in Asia is usually low in comparison with other regions [25]. The recovery of some rare agents such as *Enterobacter cloacae* complex [2], *Stenotrophomonas maltophilia* [26], *Elizabethkingia meningoseptica* [28], *Listeria monocytogenes* [21], *Enterococcus faecium* [13], *Bacillus cereus* [20] has been reported elsewhere.

The second objective of our study is to determine the antimicrobial pattern of agents causing neonatal sepsis. Results in Tables 3 and 4 show that: (1) antibiotic resistance was common for bacterial agents while all fungal isolates were sensitive to the tested antifungal, (2) vancomycin and fluoroquinolone were very effective against GP bacteria while piperacillin + tazobactam, aztreonam, and ertapenem were potent drugs against GN organisms.

The resistance to antibiotics commonly used for empirical therapy such as fluoroquinolones and  $\beta$ -lactams (carbapenems, cephalosporins, and penicillins) [9, 27, 42] occurs in almost all bacterial species

despite a small number of the tested isolates. The decreased susceptibility of bacteria to these drugs in the present study follows the trend described previously and may pose a further challenge to clinical practice in Vietnam [23, 37, 39]. In contrast, antifungal resistance was not observed among all fungal isolates. The absence of antifungal resistance could be due to the predominance of *C. albicans* in the current study, a species with rare antifungal resistance [32].

Among the tested antibiotics, vancomycin and fluoroquinolone were very effective against GP bacteria while piperacillin + tazobactam, aztreonam, and ertapenem were potent drugs against GN organisms. The potent efficacy of vancomycin against GP isolates in our study is in line with some other reports [23, 37, 39]. On a global scale, resistance to vancomycin among GP organisms is very rare [1]. It is worth noting that GP isolates in the present study seemed to have higher rates of sensitivity to fluoroquinolones (90.0–95.2%) than that in prior studies done in Vietnam (75–78%) [23, 36] and Myanmar (72.3–77%) [28]. In contrast, GN isolates demonstrated moderate susceptibility to fluoroquinolones but high sensitivity to piperacillin + tazobactam, aztreonam, and ertapenem. The moderate sensitive rate of GN organisms to fluoroquinolone in the current study (60.0–69.2%) was in the range of those reported from 13 hospitals in Vietnam (between 18–62%) [39]. The potent efficacy of ertapenem, a drug belonging to the carbapenem class, replicates findings from prior studies [23, 36, 39]. The susceptibility profile of GN bacteria to piperacillin + tazobactam

in Vietnam is limited but a study carried out in Brazil found comparable results with our study [30]. Aztreonam is the only monobactam currently approved by the FDA and selectively active against GN bacteria [10], however, this drug has rarely been used in Vietnam [9, 27, 39]. These results may have practical implications for clinicians when instituting antimicrobial therapy.

## Conclusion

In conclusion, our data showed the majority of neonatal sepsis was early-onset sepsis. Gram-negative bacteria were predominant in neonatal sepsis and early-onset sepsis while late-onset septicemia is mainly caused by Gram-positive pathogens. Antibiotic resistance was common but antifungal resistance was not reported. Vancomycin and fluoroquinolone were very effective against Gram-positive organisms while piperacillin + tazobactam, aztreonam, and ertapenem were potent drugs against GN organisms. These findings suggest the selection of empirical antimicrobials when neonatal sepsis is suspected or proven. Routine investigation of microbial profiles and antimicrobial susceptibility patterns is essential to guiding strategies for the choices of empirical antimicrobials.

## Conflict of interest

The authors declare that they have no conflict of interests.

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