*RESEARCH ARTICLE*

*ISSN 2307-9266 e-ISSN 2413-2241*

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)



# Microbiological landscape and parameters of antibiotic resistance of pathogens in patients of neonatal intensive care units

**O.I. Butranova[1], A.A. Gorbacheva[1, 2], S.K. Zyryanov[1, 3], O.G. Ni[2]**

[1] Peoples' Friendship University (RUDN University),
6 Miklukho-Maklaya Str., Moscow, Russia, 117198
[2] Kommunarka Center,
8/3 Sosenskiy Stan Str., Moscow, Russia, 108814
[3] City Clinical Hospital No. 24,
10 Pistsovaya Str., Moscow, Russia, 127015

E-mail: butranova-oi@rudn.ru

Received 26 Nov 2024 After peer review 20 Dec 2024 Accepted 30 Dec 2024

Neonatal infections remain one of the significant causes of infant mortality in the world. The change in the spectrum of pathogens, as well as their sensitivity to the main antibacterial drugs (ABDs), is a dynamically occurring process, characterized by a gradual increase in the proportion of the most dangerous pathogens, in particular, those belonging to the ESKAPE pathogen group. The study of the structure of pathogens and the parameters of their antibiotic resistance is the main tool for increasing the effectiveness of antibiotic therapy.

**The aim**. To analyze the structure of pathogens of nosocomial infections in patients of neonatal intensive care units (NICU) and assess the parameters of their antibiotic resistance.

**Materials and methods**. A retrospective epidemiological study of data from May 1, 2022 to May 1, 2024 of the laboratory information system LIS-Alice of the Kommunarka Center (Moscow, Russia) and medical documentation of patients with identified growth of microorganisms (MOs) in bacteriological cultures was carried out.

**Results.** The total number of crops was 5179, MOs growth was noted in 39.3% (*n*=2036) obtained from 734 patients, of which 87.1% were premature. Gram-positive pathogens were found in 59.6%. The top 5 identified MOs were: *S. epidermidis* (*n*=386 — 19%), *S. haemolyticus* (*n*=264 — 13%), *S. aureus* (*n*=218 — 10.7%), *K. pneumoniae* (n=210 - 10.3%) and *E. coli* (*n*=188 — 9.2%). The proportion of MOs belonging to the ESKAPE group was 28.6% (*S. aureus* — 10.7%; *K. pneumoniae* — 10.3%; *Enterobacter spp.* — 3.6%; *P. aeruginosa* — 2.3%; *A. baumannii* — 1.1%; *E. faecium* — 0.5%). Among *Staphylococcus spp*. — 71.2% were resistant to oxacillin, 53.9% — to gentamicin. At the same time, 100% sensitivity to any of the tested ABDs was not detected. The highest rates of resistance to oxacillin were observed in *S. epidermidis* (93.8%) and *S. haemolyticus* (86.7%). Also, 17% of *S. aureus* strains were resistant to oxacillin. Among *K. pneumonia* 48.8% were resistant to ceftazidime and 100% to ampicillin; *E. coli* 28.2% of strains were resistant to ceftazidime, 64.9% to ampicillin, 28.2% to sulfamethoxazole trimethoprim.

**Conclusion.** We found a high frequency of pathogen isolation (with a predominance of gram-positive pathogens) in newborns hospitalized in the ICU (mean gestational age <35 weeks). The results demonstrate alarming trends in relation to MOs resistance parameters and indicate the need for dynamic monitoring of the sensitivity of pathogens to the main ABDs used in the ICU.

**Keywords:** pathogens of neonatal infection; antibiotic resistance; neonatal sepsis; ESKAPE group; *Staphylococcus spp.*, *Klebsiella spp.*, *Escherichia coli*

**Abbreviations:** ABDs — antibacterial drugs; BAL — bronchoalveolar lavage; CI — confidence interval; CoNS — coagulase-negative staphylococci; LIS — laboratory information system; MOs — microorganisms; NS — neonatal sepsis; ICU — intensive care unit; OR — odds ratio; EDA — endotracheal aspirate; MALDI-TOF - matrix-assisted laser desorption / ionization.

**For citation:** O.I. Butranova, A.A. Gorbacheva, S.K. Zyryanov, O.G. Ni. Microbiological landscape and parameters of antibiotic resistance of pathogens in patients of neonatal intensive care units. *Pharmacy & Pharmacology.* 2024;12(6):378-393. **DOI:** 10.19163/2307-9266-2024-12-6-378-393



**Для цитирования:** О.И. Бутранова, А.А. Горбачева, С.К. Зырянов, О.Г. Ни. Микробиологический пейзаж и параметры антибиотикорезистентности возбудителей у пациентов отделений реанимации и интенсивной терапии новорожденных. *Фармация и фармакология.* 2024;12(6):378-393. **DOI:** 10.19163/2307-9266-2024-12-6-378-393

Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ
(PHARMACY & PHARMACOLOGY)

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-378-393

# Микробиологический пейзаж и параметры антибиотикорезистентности возбудителей у пациентов отделений реанимации и интенсивной терапии новорожденных

**О.И. Бутранова[1], А.А. Горбачева[1, 2], С.К. Зырянов[1, 3], О.Г. Ни[2]**

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Российский университет дружбы народов имени Патриса Лумумбы», Россия, 117198, г. Москва, ул. Миклухо-Маклая, д. 6
[2] Государственное бюджетное учреждение здравоохранения города Москвы «Московский многопрофильный клинический центр «Коммунарка» Департамента здравоохранения города Москвы», Россия, 108814, г. Москва, ул. Сосенский Стан, д. 8/3
[3] Государственное бюджетное учреждение города Москвы «Городская клиническая больница № 24 Департамента здравоохранения города Москвы», Россия, 127015, г. Москва, ул. Писцовая, д. 10

E-mail: butranova-oi@rudn.ru

Получена 26.11.2024 После рецензирования 20.12.2024 Принята к печати 30.12.2024

Неонатальные инфекции остаются одной из значимых причин младенческой смертности в мире. Изменение спектра возбудителей, а также их чувствительности к основным антибактериальным препаратам (АБП) является динамически протекающим процессом, характеризующимся постепенным ростом удельного веса наиболее опасных возбудителей, в частности, относящихся к группе ESKAPE-патогенов. Изучение структуры патогенов и параметров их антибиотикорезистентности является основным инструментом повышения эффективности антибиотикотерапии.

**Цель**. Проанализировать структуру возбудителей нозокомиальных инфекций пациентов отделений реанимации и интенсивной терапии (ОРИТ) новорождённых и оценка параметров их антибиотикорезистентности.

**Материалы и методы.** Проведено ретроспективное эпидемиологическое исследование данных за период с 1 мая 2022 по 1 мая 2024 гг. лабораторной информационной системы ЛИС-Алиса ГБУЗ «ММКЦ «Коммунарка» ДЗМ и медицинской документации пациентов с выявленным ростом микроорганизмов (МО) в бактериологических посевах.

**Результаты.** Общее число посевов составило 5179. Рост МО отмечен в 39,3% (*n*=2036) — были получены от 734 пациентов, из них 87,1% — недоношенные). Грамположительная микрофлора обнаружена в 59,6%. Топ-5 идентифицированных МО составили: *S. epidermidis* (*n*=386 — 19%), *S. haemolyticus* (*n*=264 — 13%), *S. aureus* (*n*=218 — 10,7%), *K. pneumoniae* (*n*=210 — 10,3%) и *E.coli* (*n*=188 — 9,2%). Доля МО, относящихся к группе ESKAPE, составила 28,6% (*S. aureus* — 10,7%; *K. pneumoniae* — 10,3%; *Enterobacter spp.* — 3,6%; *P. aeruginosa* — 2,3%; *A. baumannii* — 1,1%; *E. faecium* — 0,5%). Среди *Staphylococcus spp.* — 71,2% были резистенты к оксациллину, 53,9% — к гентамицину. При этом 100% чувствительности ни к одному из протестированных АБП выявлено не было. Максимально высокие показатели резистентности к оксациллину имели *S. epidermidis* (93,8%) и *S. haemolyticus* (86,7%). Также 17% штаммов *S. aureus* были резистентны к оксациллину. Среди *K. pneumonia* 48,8% были резистентны к цефтазидиму и 100% — к ампициллину; *E. coli* 28,2% штаммов были резистентны к цефтазидиму, 64,9% — к ампициллину, 28,2% — к сульфаметоксазолу / триметоприму.

**Заключение. Установлена высокая частота** выделения патогенов (с преобладанием грамположительной микрофлоры) у новорождённых, госпитализированных в ОРИТ (средний гестационный возраст <35 нед.). Результаты демонстрируют тревожные тенденции в отношении параметров резистентности МО и свидетельствуют о необходимости динамического мониторинга чувствительности возбудителей к основным АБП, применяющимся в ОРИТ.

**Ключевые слова:** возбудители инфекции новорождённых; антибиотикорезистентность; неонатальный сепсис; группа ESKAPE; стафилококки; клебсиеллы; кишечная палочка

**Список сокращений:** АБП — антибактериальные препараты; БАЛ — бронхоальвеолярный лаваж; ДИ — доверительный интервал; КНС — коагулазонегативные стафилококки; ЛИС — лабораторно-информационная система; МО — микроорганизмы; НС — неонатальный сепсис; ОРИТ — отделение реанимации и интенсивной терапии; ОШ — отношение шансов; ЭДТА — эндотрахеальный аспират; MALDI-TOF — матрично-активированная лазерная десорбция / ионизация.

## INTRODUCTION

Neonates are a special category of patients whose physiological characteristics and pathological processes determine high risks of infection with various pathogens, primarily bacterial ones. In turn, neonatal infections have a significant negative prognosis both in the short term (prolonged hospitalization, development of sepsis, death) [1–4] and in the long term perspective. Published data reveal a high risk of damage to the central nervous system in newborns with severe

infections in the first days after birth, which leads to disruptions in further development [5]. Studies have demonstrated a decrease in cognitive and motor functions, as well as hearing in children who have suffered neonatal infections [6]. It was established that neonatal sepsis (NS) is a risk factor for the development of severe functional disabling disorders in children aged 24 months (odds ratio, OR=3.68, 95% confidence interval, CI: from 1.2 to 11.2, $p$=0.021) [7]. NS occurs significantly more often in the presence of infection in the mother, during invasive procedures, and premature rupture of membranes [8–10]. The newborn characteristics as primarily gestational age and weight deserve special attention. A meta-analysis of 15 studies determined that OR for the development of NS at a gestational age of less than 37 weeks is 2.05 (95% CI: from 1.40 to 2.99), and with premature rupture of membranes — 11.14 (95% CI: from 5.54 to 22.38) [11]. Another meta-analysis identified a significant links between the development of NS and low birth weight (OR=1.42 (95% CI: from 1.07 to 1.88)) [12]. In a retrospective analysis of medical records of newborns, low birth weight and low gestational age were identified as independent risk factors for severe nosocomial infections [13].

In terms of assessing the role of pathogens, it is necessary to note the role of colonization of pregnant women with various microorganisms (MOs). Thus, in the work of Olenev et al. (2022), the widespread colonization of group B streptococcus and its significant negative consequences for newborns were demonstrated [14]. Published data established a link between infection with certain pathogens and an increased risk of developing NS [15]. Bacterial pathogens associated with early NS include primarily group B streptococci, *Escherichia coli*, *Listeria monocytogenes*, *Klebsiella* spp., *Pseudomonas* spp. and *Haemophilus influenzae* [15–17]. An association with the development of late NS has been demonstrated for coagulase-negative staphylococci (CNS), Staphylococcus aureus, the above-mentioned gram-negative pathogens, and Enterobacter spp [15, 18].

Microbiological monitoring of newborns at risk for infection (preterm low birth weight infants) is an important tool for reducing infant mortality [19]. Published data indicate that approximately 67,000 newborns die worldwide every day, with neonatal infections playing a significant role [20]. According to data collected within the framework of the CHAMPS — a global program for monitoring the health of children in regions with the highest infant mortality[1] — the most common cause of death in newborns were infections (40%). The second place was determined for prematurity (32%) and the third for respiratory distress syndrome (28%) [21]. Timely detected pathogens and the study of their antibiotic resistance parameters are an important condition for the effectiveness of antibiotic therapy and, accordingly, a positive clinical outcome.

**THE AIM.** To analyze the structure of pathogens of nosocomial infections in patients of neonatal intensive care units and to assess the parameters of their antibiotic resistance.

## MATERIALS AND METHODS

### Study design

A retrospective epidemiological study was conducted using data from the LIS-Alice laboratory information system (search keywords: “NICU-1”, “NICU-2”; total number of identified cultures — 5179) of the State Budgetary Healthcare Institution “MMCC “Kommunarka” of the Moscow Health Department, as well as medical documentation of patients who had a detected growth of MOs in bacteriological cultures ($n$=734). The study period was from May 1, 2022 to May 1, 2024.

NICU-1 is a neonatal intensive care unit of the first stage of nursing. Admission criteria: newborns with very low (<2.5 kg) and extremely low body weight (<1 kg), low gestational age, in critical condition in the neonatal period, especially with acute respiratory failure.

NICU-2 is a neonatal intensive care unit of the second stage of nursing. Admission criteria: patients after stabilization of their condition in NICU-1 (requiring a stay in the ICU for more than 7 days), admitted for further nursing, as well as patients transferred from the neonatal pathology unit due to deterioration of their condition (development of respiratory failure, heart failure requiring vasopressor support, condition after surgery).

### Research methodology

LIS-Alice (locus of material collection, presence of growth, pathogen, data on its sensitivity / resistance to ABP) was used as a source of data on patient cultures and identified parameters of antibiotic resistance. Patient medical histories (gender, age, body weight, Apgar score at birth) were used as a source of demographic, anthropometric and clinical data. The collecting of samples was carried out by physicians as part of standard patient management (upon admission to the

[1] Child Health and Mortality Prevention Surveillance. – [Электронный ресурс]. – Режим доступа: https://champshealth.org/

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-378-393

NICU for the purpose of microbiological monitoring, as well as in case of signs of infection). For the identification of MOs, the MALDI-TOF mass spectrometry (matrix-assisted laser desorption/ ionization) method was used in the microbiology laboratory. Sensitivity to antibacterial drugs was determined by the automated disk diffusion method.

### Ethics approval

The study approval from Local Ethics Committees of the Medical Institute of the Peoples' Friendship University of, extract from Protocol No. 24 dated January 18, 2024; Moscow Multidisciplinary Clinical Center "Kommunarka, extract from Protocol No. 2 dated 13.02.2024).

### Statistical processing

Statistical data processing was performed using Microsoft Excel 2019 software. Descriptive statistics were used for all analyzed indicators (mean and standard deviation (SD), minimum (min) and maximum values (max), median (Me), interquartile range (IQR) were determined). Qualitative variables were described using absolute (*n*) and relative (%) values.

## RESULTS

The total number of cultures identified during the study period (two years) was 5179. Of these, microbial growth was observed in 39.3% (*n*=2036). One MO was detected in 74.3% of cultures (*n*=545); 2 or more MOs — in 25.7% (*n*=189).

The total number of patients from whom cultures with growth were obtained was 734. Of these, 87.1% were premature infants (*n*=639). The average Apgar score at 1 minute was 4.9±2.2 (min=1, max=8, Me=5, IQR=1.9); at 5 min 6.0±1.6 (min=3, max=9, Me=6). Female gender was in 66.6% (*n*=489), male in 33.4% (*n*=245).

The mean gestational age of the total population of neonates according to medical records was 34.6±4.8 weeks (min=20.4 weeks, max=54.3 weeks, Me=35.1 weeks, IQR=8.8). The mean birth weight was 2970.7±1271.9 g (min=360, max=4125, Me=3705, IQR=1746.5). Extremely low birth weight (<1000 g) was observed in 14.2% (*n*=104), very low (1000–1499 g) —in 26.7% (*n*=196), low (1500–2499 g) — in 21.1% (*n*=155), normal (>2500 g) — in 38% (*n*=279).

Patient characteristics depending on hospitalization in NICU-1 and NICU-2 are presented in Table 1.

The mean duration of hospitalization at the time of detection of MO was 12.6±12.4 (min=0, max=97.3, Me=6, IQR=17.1) days.

In the overall structure of cultures (both with and without growth), the analysis of the loci of biomaterial collection revealed the dominance of samples from the pharynx (*n*=2669, 51.5%, of which growth-positive were 1434, 53.7%). Next came blood (*n*=1431, 27.6%, of which growth-positive were 170, 11.8%) and endotracheal aspirate (*n*=451, 8.7%, of which growth-positive were 180, 39.9%). Among the cultures with detected growth, the pharyngeal swab was leader (*n*=1334, 65.5%), the second place was determined for the rectal swab (*n*=212, 10.4%), and the third for the endotracheal aspirate swab (*n*=181, 8.9%). The contribution of each locus to the total structure of cultures is presented in Table 2.

The next stage of the analysis was devoted to assessing the proportion of gram-positive and gram-negative MOs in the overall structure. Gram-positive microflora was detected in 59.6% (*n*=1213), gram-negative — in 40.4% (*n*=823). The proportion of detected gram-positive and gram-negative MOs depending on the locus of biomaterial collection is presented in Figure 1.

We found a predominance of gram-positive MOs in the blood (*n*=143, 89.4%) and pharyngeal swab (*n*=821, 61.5%), while gram-negative microorganisms dominated in endotracheal aspirate (EDTA; *n*=105, 58.0%) and rectal swab (*n*=118, 55.7%)

In the overall structure of MOs, the absolute predominance was detected for *Staphylococcus* spp. (46.2%), and second were isolates of *Klebsiella* spp. (15.32%). The main groups of microorganisms identified as a result of the analysis are presented in Figure 2.

Studying the spectrum of MOs isolated from various loci, it was found that for pharyngeal swabs and blood samples, the first place among all pathogens was occupied by strains of *S. epidermidis*, while in the rectal swab and EDTA the leader was *K. pneumoniae*. It is noteworthy that in EDTA the second place in terms of detection frequency belonged to a rather rare pathogen, *Stenotrophomonas maltophilia*, while the first place was shared by *K. pneumoniae* and *S. epidermidis* (13.8% for each), a detailed picture is presented in Figure 3.

The analysis of the isolated pathogens revealed a large proportion of representatives of the ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.). The proportion of cultures with ESKAPE pathogens was 28.6% (*n*=582). The structure of the ESKAPE MOs identified in our study is presented in Figure 4.

Determination of the frequency of occurrence

of each pathogen in the overall structure of cultures allowed us to determine the top five pathogens identified in neonates in the NICU. They included *S. epidermidis* (*n*=386; 19%), *S. haemolyticus* (*n*=264; 13%), *S. aureus* (*n*=218; 10.7%), *K. pneumoniae* (*n*=210; 10.3%) and *E. coli* (*n*=188; 9.2%).

The detailed structure of pathogens identified in samples from different loci is presented below. Staphylococci were the leading pathogens in pharyngeal swabs (48.9%). Information on the proportion of other pathogens identified from this locus is presented in Table 3.

In the rectal swabs, gram-negative microflora dominated. However, assessing the contribution of each MO, we registered that the first place belonged to staphylococci (31.6%), and *Klebsiella* spp. occupied the second place (29.2%). The overall structure of pathogens detected in rectal swabs is presented in Table 4.

In the general structure of pathogens detected in EDTA swabs, *Staphylococcus* spp. (26.0%) and *Klebsiella* spp. (20.4%) also led. The general structure of pathogens detected in EDTA is presented in Table 5.

The blood samples showed a predominance of gram-positive MOs, with the proportion of staphylococci in the overall structure being 73.8%. Detailed data on the structure of pathogens detected in the blood are presented in Table 6.

The next stage of our work was devoted to assessing the sensitivity of the identified MOs to ABDs. Since the main gram-positive MOs were staphylococci, enterococci, streptococci and corynebacteria, below we present the results of a combined analysis of sensitivity to ABDs for these groups of pathogens (Table 7). The most significant results included the detection of staphylococcal resistance: 71.2% of all strains were resistant to oxacillin and more than half of the strains were resistant to gentamicin (53.9%).

The results of the analysis of the sensitivity of the main gram-negative pathogens to different ABDs are presented in Table 8. They demonstrated a higher conditional average level of antibiotic resistance compared to gram-positive pathogens. 88.9% of *Klebsiella* spp. strains were resistant to ampicillin, more than a third — to the third-generation cephalosporin ceftazidime (34.7%). Mentioned ABDs are also of interest in terms of E. coli resistance: 64.9% of strains were resistant to the first, 28.2% to the second. For *Acinetobacter* spp. and *Enterobacter* spp., we did not find significant changes in sensitivity to ABDs. For *P. aeruginosa*, the analysis established trends towards increasing resistance to all tested ABDs.

The top MOs in the structure were *S. epidermidis* and *S. haemoliticus*. The study of their ABDs sensitivity revealed a significant proportion of oxacillin-resistant strains (93.8 and 86.7%, respectively) and gentamicin-resistant strains (70.2 and 80.2%, respectively), detailed data are presented in Table 9.

Among the identified pathogens, almost a third belonged to the ESKAPE group. These MOs usually cause severe infectious processes, and their presence is usually accompanied by a high level of antibiotic resistance. In this regard, we conducted a separate analysis of the sensitivity parameters of *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter* spp.; the results are presented in Table 10 (for gram-positives) and Table 11 (for gram-negatives).

Considering that the pathogens to the ESKAPE group were determined in different loci, which implies different localization of the infectious process and may also indicate the degree of its generalization, we then conducted a comparative analysis of the antibiotic resistance of individual MOs of this group depending on the source of biomaterial collection (*A. baumannii* was not included in the analysis, since no significant changes in sensitivity in the overall structure were found for it). The results revealed the highest resistance rates of gram-positive MOs in endotracheal aspirate samples. *K. pneumoniae* strains showed a fairly high resistance to ceftazidime in all samples, and 100% resistance to ampicillin. The most resistant *P. aeruginosa* strains were isolated primarily from samples obtained from rectal swabs. Detailed information is presented in Figures 5–8.

## DISCUSSION

Our results revealed that population of patients hospitalized in the NICU was represented mainly by premature neonates (87.1%) with low birth weight (birth weight ≤ 2499 g was detected in 62%). Accordingly, most patients were at risk of infection with bacterial pathogens. In general, published data indicate a fairly high incidence of nosocomial infections in premature infants (gestational age<32 weeks, birth weight <1500 g): from 5.6% to 34.4% during the first 120 days of life [22]. The localization and type of infections are variable, but the most common in the global practice of neonatal care are bloodstream infections (frequency from 5.6 per 1000 days of central venous catheter use to 7.3 per 1000 days of umbilical catheter use) [23], and ventilator-associated pneumonia (frequency 7.8 per 1000 days of artificial ventilation use) [24].

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-378-393

**Table 1 – Characteristics of patient with growth-positive cultures**

| Parameter | NICU-1 (*n*=311) | NICU-2 (*n*=423) |
|---|---|---|
| Age at the time of hospitalization, weeks | | |
| M + SD | 33.8±4.5* | 36.7±5.1** |
| min | 20.4 | 27.0 |
| max | 41.6 | 54.3 |
| Me (IQR) | 35.0 (9.3) | 35.5 (7.9) |
| Body weight at the time of hospitalization, g | | |
| M+SD | 2185.2±1022.8 | 2269.0±926.8 |
| min | 360.0 | 661.0 |
| max | 3940.0 | 4125.0 |
| Me (IQR) | 2074.5 (1943.5) | 2117.5 (1982.5) |

Note: * gestational age; ** postconceptual age. NICU — neonatal intensive care unit.

**Table 2 – Contribution of each locus to the structure of cultures**

| Locus | Culture-negative + culture-positive | | Culture-positive | |
|---|---|---|---|---|
| | *n* (total 5179) | % | *n* (total 2036) | % |
| Pharynx | 2669 | 51.5 | 1334 | 65.5 |
| Rectum | 362 | 7.0 | 212 | 10.4 |
| Endotracheal aspirate | 451 | 8.8 | 181 | 8.9 |
| Blood | 1431 | 27.6 | 160 | 7.9 |
| Urine | 137 | 2.6 | 97 | 4.8 |
| Vascular catheter | 94 | 1.8 | 24 | 1.2 |
| Skin | 25 | 0.5 | 20 | 1.0 |
| Other (CSF, BAL, gastric contents, conjunctival secretions) | 10 | 0.2 | 8 | 0.4 |

Note: BAL — bronchoalveolar lavage.

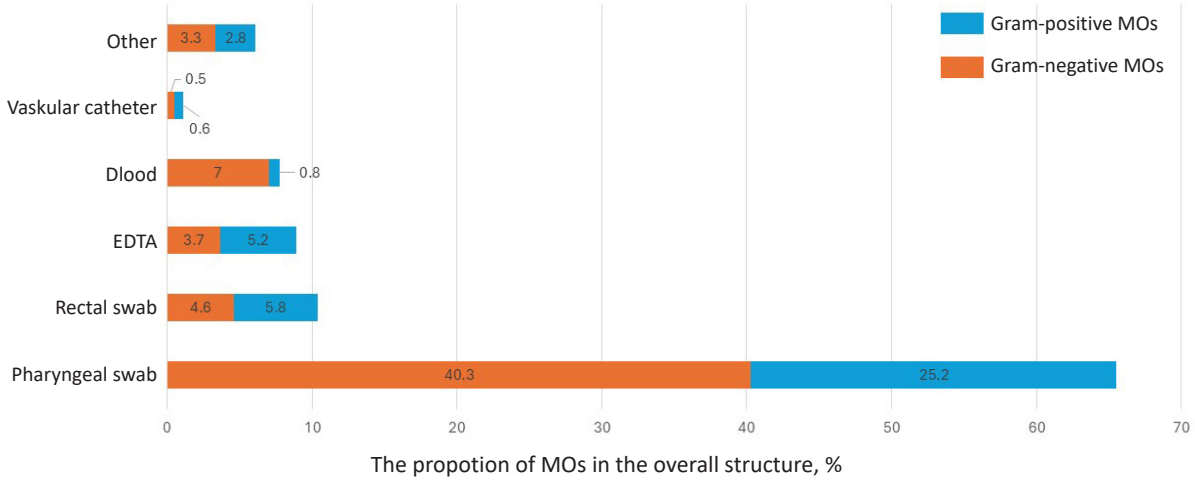


**Figure 1 – The proportion of detected gram-positive and gram-negative Mos depending on the locus of biomaterial collection.**

Note: EDTA — endotracheal aspirate; MOs — microorganisms.

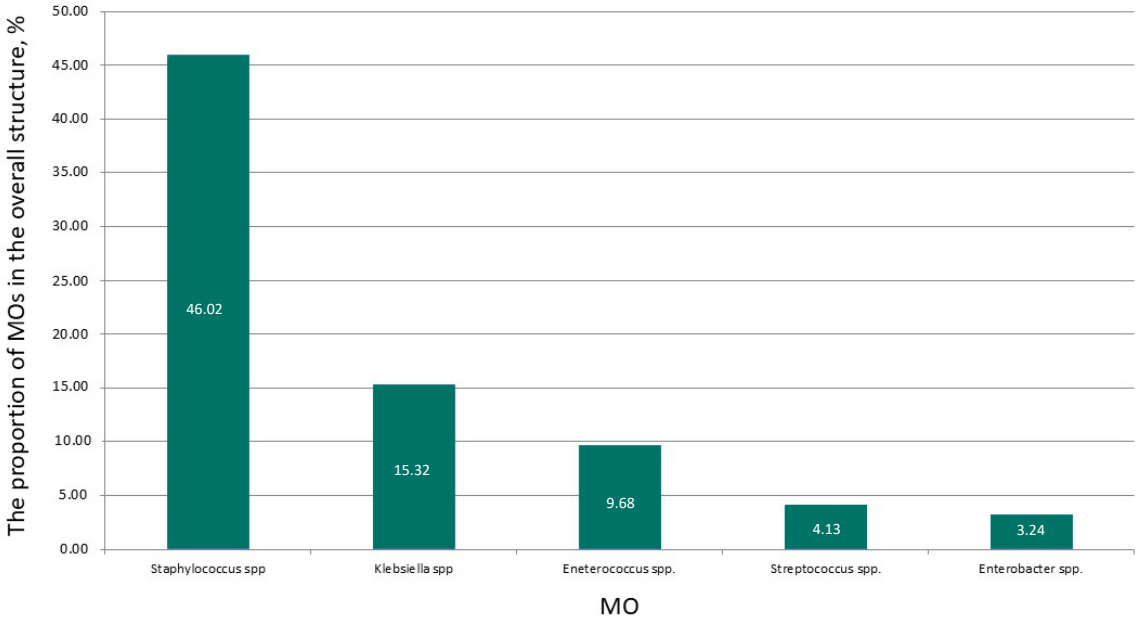


**Figure 2 – The main groups of MOs identified in the analysis of neonatal cultures in the neonatal intensive care units.**

Note: MOs — microorganisms.

**Table 3 – Structure of pathogens identified in throat swabs**

| Pharyngeal swab | *n* (total 1334) | % |
|---|---|---|
| Gram-positive MOs | 821 | 61.5 |
| *Staphylococcus* spp.: | 652 | 48.9 |
| • *S. epidermidis* | 250 | 18.7 |
| • *S. haemoliticus* | 205 | 15.4 |
| • *S. aureus* | 162 | 12.1 |
| • *S. hominis* | 26 | 1.9 |
| • *S. lugdunensis* | 8 | 0.6 |
| • *S. capitis* | 1 | 0.1 |
| *Enterococcus* spp.: | 102 | 7.6 |
| • *E. faecalis* | 97 | 7.3 |
| • *E. faecium* | 5 | 0.4 |
| *Streptococcus* spp.: | 54 | 4.0 |
| • *S. agalactiae* | 49 | 3.7 |
| • *S. anginosus* | 8 | 0.6 |
| *Corynebacterium* spp. | 10 | 0.7 |
| *Listeria monocytogenes* | 3 | 0.2 |
| Gram-negative MOs | 513 | 38.5 |
| *Klebsiella* spp.: | 189 | 14.2 |
| • *K.pneumoniae* | 128 | 9.6 |
| • *K. oxytoca* | 42 | 3.1 |
| • *K. variicola* | 1 | 0.1 |
| • *K. aerogenes* | 18 | 1.3 |
| *E. coli* | 167 | 12.5 |
| *Enterobacter* spp. | 49 | 3.7 |
| *Acinetabacter* spp.: | 33 | 2.5 |
| • *A. baumannii* | 18 | 1.3 |
| • *A. albensis* | 1 | 0.1 |
| • *A. pittii* | 6 | 0.4 |
| *Stenotrophomonas maltophilia* | 24 | 1.8 |
| *P. aeruginosa* | 20 | 1.5 |
| *Citrobacter* spp. | 20 | 1.5 |
| *H. influenzae* | 7 | 0.5 |
| *P. mirabilis* | 3 | 0.2 |
| *Morganella morganii* | 1 | 0,1 |

Note: MOs — microorganisms.

**Table 4 – Overall structure of pathogens detected in rectal swabs**

| Rectal swab | *n* (total 212) | % |
|---|---|---|
| Gram-positive MOs | 94 | 44.3 |
| *Staphylococcus* spp.: | 67 | 31.6 |
| • *S. epidermidis* | 24 | 11.3 |
| • *S. aureus* | 22 | 10.4 |
| • *S. haemoliticus* | 20 | 9.4 |
| • *S. warneri* | 1 | 0.5 |
| *Enterococcus* spp.: | 27 | 12.7 |
| • *E. faecalis* | 19 | 9.0 |
| • *E. faecium* | 8 | 3.8 |
| Gram-negative MOs | 118 | 55.7 |
| *Klebsiella* spp.: | 62 | 29.2 |
| • *K. Pneumoniae* | 44 | 20.8 |
| • *K. Oxytoca* | 11 | 5.2 |
| • *K. Aerogenes* | 7 | 3.3 |
| *P. aeruginosa* | 17 | 8.0 |
| *E. coli* | 12 | 5.7 |
| *Acinetobacter* spp.: | 4 | 1.9 |
| • *A. lwoffii* | 1 | 0.5 |
| • *A. baumannii* | 1 | 0.5 |
| *Enterobacter* spp. | 14 | 6.6 |
| *Stenotrophomonas maltophilia* | 4 | 1.9 |
| *Serratia* spp. | 3 | 1.4 |
| *Proteus* spp. | 2 | 0.9 |

Note: MOs — microorganisms.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-378-393

**Table 5 – General structure of pathogens detected in endotracheal aspirate**

| EDTA | *n* (total 181) | % |
|---|---|---|
| Gram-positive MOs | 76 | 42.0 |
| *Staphylococcus* spp.: | 47 | 26.0 |
| • *S. epidermidis* | 25 | 13.8 |
| • *S. aureus* | 14 | 7.7 |
| • *S. haemoliticus* | 8 | 4.4 |
| *Streptococcus* spp.: | 14 | 7.7 |
| • *S. agalactiae* | 10 | 5.5 |
| • *S. anginosus* | 1 | 0.6 |
| • *S. gordonii* | 1 | 0.6 |
| • *S. salivarius* | 1 | 0.6 |
| • *S. lutetiensis* | 1 | 0.6 |
| *Enterococcus* spp.: | 8 | 4.4 |
| • *E. faecalis* | 7 | 3.9 |
| • *E. faecium* | 1 | 0.6 |
| *Corynebacterium* spp. | 4 | 2.2 |
| *Listeria monocytogenes* | 3 | 1.7 |
| Gram-negative MOs | 105 | 58.0 |
| *Klebsiella* spp.: | 37 | 20.4 |
| • *K. pneumoniae* | 25 | 13.8 |
| • *K. aerogenes* | 10 | 5.5 |
| • *K. oxytoca* | 7 | 3.9 |
| *Stenotrophomonas maltophilia* | 18 | 9.9 |
| *P. aeruginosa* | 14 | 7.7 |
| *Enterobacter* spp.: | 10 | 5.5 |
| *E. coli* | 8 | 4.4 |
| *Serratia* spp. | 6 | 3.3 |
| *Acinetobacter* spp. | 5 | 2.8 |
| • *A. baumannii* | 3 | 1.7 |
| • *A. junii* | 2 | 1.1 |
| *Citrobacter* spp. | 3 | 1.7 |
| *H. influenzae* | 1 | 0.6 |
| *Ralstonia pickettii* | 1 | 0.6 |
| *Proteus mirabilis* | 1 | 0.6 |
| *Delftia acidovorans* | 1 | 0.6 |

Note: EDTA — endotracheal aspirate; MOs — microorganisms.

**Table 6 – Overall structure of pathogens detected in the blood samples**

| Blood | *n* (total 160) | % |
|---|---|---|
| Gram-positive MOs | 143 | 89.4 |
| *Staphylococcus* spp.: | 118 | 73.8 |
| • *S. epidermidis* | 71 | 44.4 |
| • *S. haemoliticus* | 31 | 19.4 |
| • *S. aureus* | 15 | 9.4 |
| • *S. capitis* | 1 | 0.6 |
| *Streptococcus* spp.: | 14 | 8.8 |
| • *S. agalactiae* | 9 | 5.6 |
| • *S. anginosus* | 1 | 0.6 |
| • *S. gordonii* | 1 | 0.6 |
| • *S. salivarius* | 1 | 0.6 |
| • *S. lutetiensis* | 1 | 0.6 |
| • *S. pneumoniae* | 1 | 0.6 |
| *Corynebacterium* spp. | 4 | 2.5 |
| *Enterococcus* spp.: | 4 | 2.5 |
| • *E. faecalis* | 4 | 2.5 |
| • *E. faecium* | 0 | 0.0 |
| *Listeria monocytogenes* | 3 | 1.9 |
| Gram-negative MOs | 17 | 10.6 |
| *Klebsiella* spp.: | 8 | 5.0 |
| • *K. pneumoniae* | 8 | 5.0 |
| *P. aeruginosa* | 2 | 1.3 |
| *Enterobacter* spp.: | 2 | 1.3 |
| *E. coli* | 1 | 0.6 |
| *H. influenzae* | 1 | 0.6 |
| *Acinetobacter* spp.: | 1 | 0.6 |
| • *A. baumannii* | 1 | 0.6 |
| • *A. junii* | 0 | 0.6 |
| • *A. lwoffii* | 1 | 0.6 |
| • *Citrobacter* spp. | 1 | 0.6 |

Note: MOs — microorganisms.

**Table 7 – Parameters of antibacterial drugs sensitivity of the main gram-positive microorganisms**

| ABD | Proportion (%) R/S, MOs | *Staphylococcus* spp. (*n*=894) | *Enterococcus* spp. (*n*=141) | *Streptococcus* spp. (*n*=86) | *Corynebacterium* spp. (*n*=18) |
|---|---|---|---|---|---|
| Oxacillin | R | 71.2 | NA | 0 | NA |
| | S | 28.9 | NA | 100 | NA |
| Tigecycline | R | 0.9 | 0 | 0 | NA |
| | S | 99.1 | 100 | 100 | NA |
| Vancomycin | R | 1.8 | 0 | 0 | 0 |
| | S | 98.2 | 100 | 100 | 100 |
| Linezolid | R | 0.8 | 0 | 0 | 0 |
| | S | 99.2 | 100 | 100 | 100 |
| Gentamicin | R | 53.9 | NA | NA | NA |
| | S | 46.1 | NA | NA | NA |
| Ampicillin | R | NA | 7.1 | 0 | NA |
| | S | NA | 92.9 | 100 | NA |

Note: ABDs — antibacterial drugs; MOs — microorganisms; NA — not applicable; R — resistant; S — sensitive.

**Table 8 – Parameters of antibacterial drugs sensitivity of the main gram-negative microorganisms**

| ABDs | Proportion (%) R/I/S, MOs | *Klebsiella* spp. (*n*=296) | *E. coli* (*n*=188) | *Acinetobacter* spp. (*n*=57) | *Enterobacter* spp. (*n*=75) | *P. aeruginosa* (*n*=54) |
|---|---|---|---|---|---|---|
| Amikacin | R | 5.1 | 4.8 | 0 | 2.7 | 19.5 |
| | S | 95.9 | 95.2 | 100 | 97.3 | 80.5 |
| Cefepime | R | 7.6 | 3.2 | 10.5 | 2.7 | 30.5 |
| | I | 11.1 | 0.5 | 0 | 1.3 | 82.0 |
| | S | 81.3 | 96.3 | 89.5 | 96 | 14.8 |
| Meropenem | R | 6.2 | 0 | 3.5 | 0 | 20.1 |
| | S | 93.8 | 100 | 96.5 | 100 | 53.2 |
| Ceftazidime | R | 34.7 | 28.2 | NA | 16 | 30.5 |
| | I | 12.6 | 5.3 | NA | 1.3 | 65.8 |
| | S | 52.7 | 66.5 | NA | 82.7 | 3.7 |
| Gentamicin | R | 14.3 | 4.8 | 5,3 | 4 | NA |
| | S | 85.7 | 95.2 | 94,7 | 96 | NA |
| Ampicillin | R | 88.9 | 64.9 | NA | 100 | NA |
| | S | 11.1 | 35.1 | NA | 0 | NA |
| Sulfamethoxazole trimethoprim | R | 3.7 | 28.2 | 7.0 | 0 | NA |
| | S | 96.3 | 71.8 | 93.0 | 100 | NA |

Note: ABDs — antibacterial drugs; MOs — microorganisms; NA — not applicable; R — resistant; I — intermediate; S — sensitive.

**Table 9 – Parameters of antibacterial drugs sensitivity of *S. epidermidis* and *S. haemoliticus***

| ABDs | Proportion (%) R/S, MOs | *S. epidermidis* (*n*=386) | *S. haemoliticus* (*n*=264) |
|---|---|---|---|
| Oxacillin | R | 93.8 | 86.7 |
| | S | 6.2 | 13.3 |
| Tigecycline | R | 0.8 | 0.8 |
| | S | 99.2 | 99.2 |
| Vancomycin | R | 0 | 1.5 |
| | S | 100 | 98.5 |
| Linezolid | R | 0 | 3.4 |
| | S | 100 | 96.6 |
| Gentamicin | R | 70.2 | 80.2 |
| | S | 29.8 | 19.8 |

Note: ABDs — antibacterial drugs; MOs — microorganisms; R — resistant; S — sensitive.

**Table 10 – Parameters of antibacterial drugs sensitivity of gram-positive microorganisms of the ESKAPE group**

| ABDs | Proportion (%) R/S, MOs | *S. aureus* (*n*=218) | *E. faecium* (*n*=10) |
|---|---|---|---|
| Oxacillin | R | 17.1 | NA |
| | S | 82.9 | NA |
| Tigecycline | R | 0 | 0 |
| | S | 100.0 | 100 |
| Vancomycin | R | 4.5 | 0 |
| | S | 95.5 | 100 |
| Linezolid | R | 4.2 | 0 |
| | S | 95.8 | 100 |
| Gentamicin | R | 9.2 | NA |
| | S | 90.8 | NA |
| Ampicillin | R | NA | 72.2 |
| | S | NA | 27.8 |

Note: ABDs — antibacterial drugs; MOs — microorganisms; NA — not applicable; R — resistant; S — sensitive.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-378-393

**Table 11 – Parameters of antibacterial drugs sensitivity of gram-negative microorganisms of the ESKAPE group**

| ABDs | Proportion (%) R/I/S, MOs | *K. pneumoniae* (*n*=210) | *A. baumanni* (*n*=23) | *Enterobacter* spp. (*n*=75) | *P. aeruginosa* (*n*=54) |
|---|---|---|---|---|---|
| Amikacin | R | 2.0 | 0.0 | 2.7 | 19.5 |
| | S | 98.0 | 100.0 | 97.3 | 80.5 |
| Cefepime | R | 7.6 | 17.0 | 2.7 | 22.4 |
| | I | 0.0 | 0 | 1.3 | 64.1 |
| | S | 92.4 | 83.1 | 96 | 13.5 |
| Meropenem | R | 0.6 | 0.0 | 0 | 20.1 |
| | S | 99.4 | 100.0 | 100 | 53.2 |
| Ceftazidime | R | 48.8 | NA | 16 | 30.5 |
| | I | 7.0 | NA | 1.3 | 65.8 |
| | S | 44.2 | NA | 82.7 | 3.7 |
| Gentamicin | R | 6.9 | 0.0 | 4 | NA |
| | S | 93.1 | 100.0 | 96 | NA |
| Ampicillin | R | 100.0 | NA | 100 | NA |
| | S | 0.0 | NA | 0 | NA |
| Sulfamethoxazole trimethoprim | R | 3.7 | 6.2 | 0 | NA |
| | S | 96.3 | 93.8 | 100 | NA |

Note: ABDs — antibacterial drugs; MOs — microorganisms; NA — not applicable; R — resistant; I — intermediate; S — sensitive.

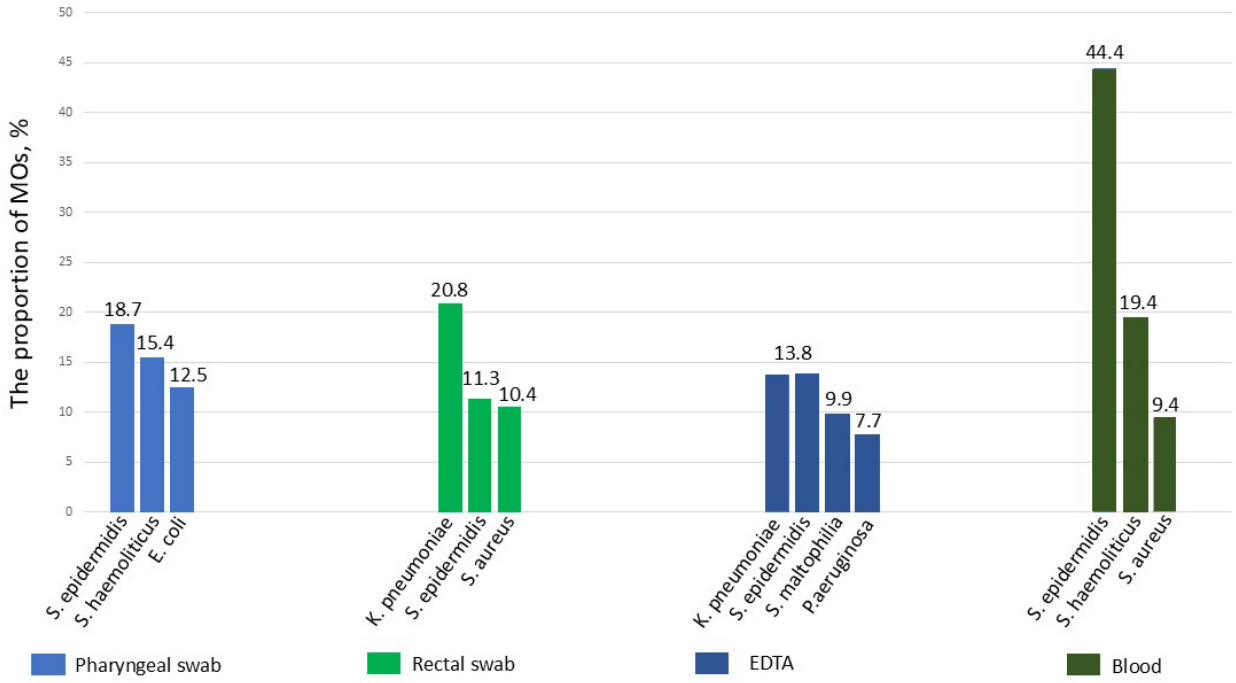


**Figure 3 – Leading microorganisms identified in the main loci of biomaterials collection.**
Note: MOs — microorganisms.

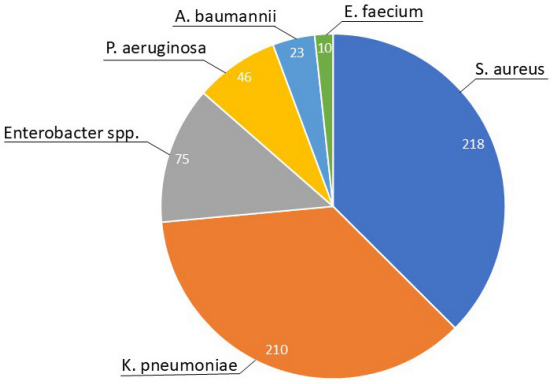


**Figure 4 – The structure of ESKAPE group pathogens.**
Note: The data is presented as absolute values.

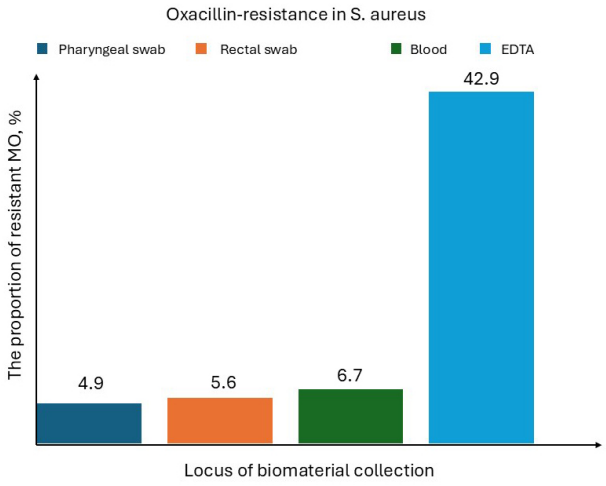


**Figure 5 – Oxacillin-resistance in *S. aureus* depending on the locus of biomaterial collection.**
Note: EDTA — endotracheal aspirate; MO — microorganism.

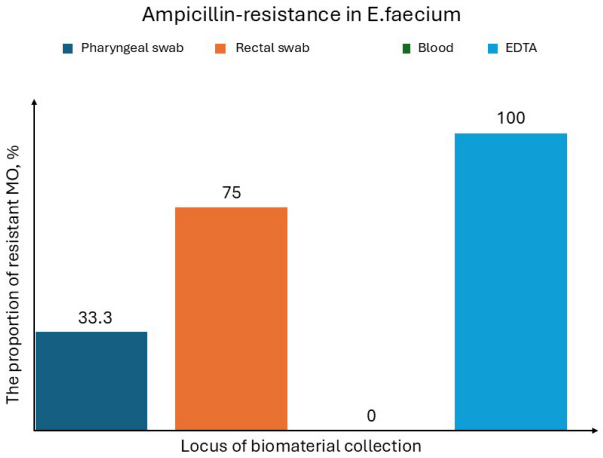


**Figure 6 – Ampicillin-resistance in *E. faecium* depending on the locus of biomaterial collection.**
Note: EDTA — endotracheal aspirate; MO — microorganism.

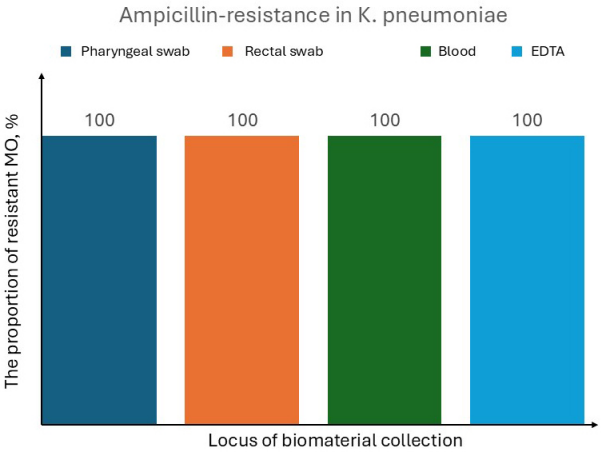


**Figure 7 – Ampicillin-resistance in *K. pneumoniae* depending on the locus of biomaterial collection.**
Note: EDTA — endotracheal aspirate; MO — microorganism.

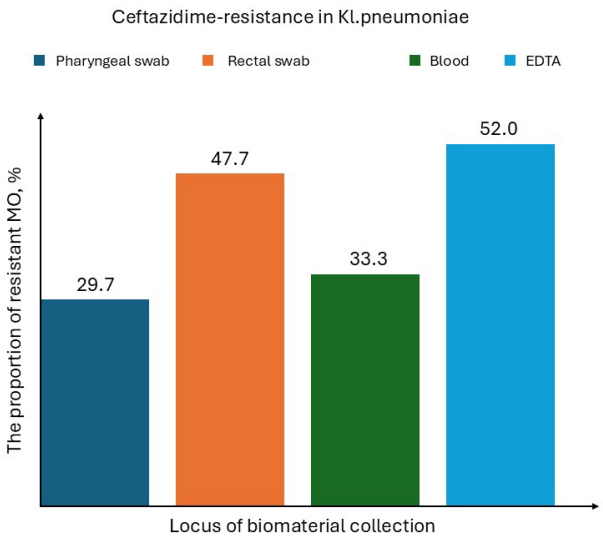


**Figure 8. Ceftazidime-resistance in *K. pneumoniae* depending on the locus of biomaterial collection.**
Note: EDTA — endotracheal aspirate; MO — microorganism.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-378-393

The localization and nature of the infectious process depend on the locus of MO identification. Our study found a predominant growth of MO in samples from non-sterile loci (pharyngeal swab, rectal swab). More attention should be paid to the fact that growth was also recorded in loci that are normally sterile: in EDTA and blood, the latter indicating the development of bacteremia and possible sepsis. According to an analysis of 451,443 newborns in the United States, the frequency of nosocomial bacteremia was 2%, unadjusted incidence rate was 1.1 per 1000 patient-days (95% CI: 1.0 to 1.2), and a significantly higher incidence for neonates weighing less than 750 g was demonstrated (14.2 per 1000 patient-days (95% CI: 12.6 to 16.1) [25].

In the structure of the identified MOs, representatives of gram-positive microflora were in the lead – 59.6% (*n*=1213). In general, this is consistent with the results of previously published studies. According to a retrospective epidemiological study lasting 11 years (Sweden, 2006–2016), gram-positive MOs were identified four times more often in newborns with bloodstream infections compared to gram-negative MOs; the most common pathogens were represented by CNS (53.8%) [26]. In a prospective cross-sectional study that included newborns with NS, gram-positive MOs were identified in 53.4% [27]. According to a retrospective analysis of the spectrum of pathogens identified in newborns with NS (China), the majority also belonged to gram-positives, while in the overall structure the authors determined the leadership of CNS (41%) [28]. Similar results were obtained in a literature review (30 sources in the final analysis): CNS as NS pathogens were identified in 40.23% [29]. The results of a study of NS pathogens, which included a 20-year period (South Korea), are indicative. They established an absolute predominance of gram-positive MOs (75.3%), among which the main contribution was also made by CNS [30]. The top 5 pathogens identified in our study included *S. epidermidis* (*n*=386, 19.0%), *S. haemolyticus* (*n*=263; 12.9%), *S. aureus* (*n*=218; 10.7%), *K. pneumoniae* (*n*=210; 10.3%) and *E. coli* (*n*=188; 9.2%). *S. epidermidis*, a representative of the CNS, is characterized by a high frequency of detection in newborns in general (being a commensal, it colonizes the skin, respiratory tract, intestines), and is also one of the main causes of late NS in premature infants [31]. Its dominance in our study may be associated with both its role in the development of infections (in most cases) and asymptomatic carriage, which is also a negative prognostic factor [32]. The level of resistance of S. epidermidis to oxacillin that we identified was 93.8%. The high frequency of detection of this pathogen in our study determined the overall high level of resistance of staphylococci to oxacillin. A retrospective analysis of data from newborns with sepsis in Sweden (period 2006–2016) indicates a high level of resistance of S. epidermidis to isoxazolylpenicillins — 91.7% [26]. According to a retrospective descriptive study of medical records of newborns admitted to the NICU (Brazil, 2015–2022, *n*=1610), infections caused by oxacillin-resistant staphylococci occurred in 12%, of which S. epidermidis was responsible for 60.1% [33]. Infections caused by oxacillin-resistant staphylococci, according to Ferreira et al (2024), are associated with prolonged hospitalization (from 10 to 46 days) and increased mortality (from 10.2% to 19.2%). The mean time from infection to death was 15 days (IQR: 8–40) [33]. According to a literature review of studies on NS, Wang et al (2022) found *S. epidermidis* to have the highest resistance to such ABDs as erythromycin and penicillin [29]

The second most frequently detected pathogen identified in our study, *S. haemolyticus*, was also characterized by an extremely high level of resistance to oxacillin, 86.7%. Being a representative of CNS, this MOs typically colonizes the skin. In modern clinical practice, most of *S. haemolyticus* strains exhibit multidrug resistance, which makes them a significant cause of severe NS [34, 35]. Representatives of the ESKAPE group were identified in a third of all cultures in our study 582 (28.6%). The significant role of ESKAPE group MOs in the genesis of infections in newborns is confirmed by many studies. Tzialla et al (2024), having analyzed the global database of outbreaks of nosocomial diseases (Outbreak Database, https://www.outbreak-database.com/Home.aspx), found that the main pathogens in newborns in the NICU were *S. aureus* (24%) and *Klebsiella* spp. (20%) [19].

The characteristics of patients with NS caused by *S. aureus* are well described in the work demonstrating the results of a retrospective study of medical records of patients over a 20-year period (Australia) [36]. The overall incidence was 0.10 per 1000 live births, the analysis found its decrease after 2011 (from 2001 to 2010 — 0.13/1000; from 2011 to 2020 — 0.07/1000). The authors identified EDTA as the main source of biomaterial for cultures that revealed the growth of this pathogen. An important discovery was the detection of a link between *S. aureus* infection and the development of subsequent neurological deterioration [36]. According to our data, the only noteworthy aspect regarding the assessment of the susceptibility parameters of *S. aureus* to ABDs was the detection of resistance to oxacillin in 17.1% of strains and to gentamicin in 9.2%. This differs from the results

obtained by Oldendorff et al (2024) for a population of newborns with sepsis in Sweden: the authors did not find a single case of resistance to isoxazolyl penicillins, nor any significant resistance to other ABDs [26]. An analysis of *S. aureus* antibiotic resistance parameters based on data from patients in a pediatric hospital in Beijing (2013–2022) revealed high levels of resistance to penicillin (89.5%) and erythromycin (73.8%) against the background of high susceptibility to linezolid, vancomycin, rifampicin, and moxifloxacin [37].

The next significant pathogen, ranking fourth in terms of detection frequency in the NICU population in our study, is *K. pneumoniae* (*n* = 210; 10.3%). This pathogen is one of the most common causes of gram-negative NS. According to Nordberg et al (2024), *K. pneumoniae* ranked second after *E. coli*, accounting for 18.7% (20 out of 107) [38]. According to our study, about half of all K. pneumoniae strains were resistant to ceftazidime (48.8%), and 100% demonstrated resistance to ampicillin. This distinguishes our data from the results of Nordberg et al (2024), who did not find significant resistance of this MOs to the tested ABDs [38], but coincides with the data obtained by You et al (2020) in a retrospective analysis of the medical records of newborns with sepsis caused by *K. pneumoniae* in China (the period from 2000 to 2019): the authors found resistance to ampicillin in 98.8%, ceftazidime in 71.5%, cefazolin in 87.2%, and cefotaxime in 82.6%. At the same time, the pathogen retained high sensitivity to aminoglycosides and fluoroquinolones. [39]. The last MO among the top 5 pathogens identified in our study was *E. coli* (*n*=188; 9.2%). In the structure of pathogens of gram-negative NS in Sweden, this MO was identified as the main one (43.9%; 47 out of 107) [38]. The main characteristics of *E. coli* revealed in our study were resistance to ceftazidime in 28.2% of strains, to ampicillin in 64.9% of strains, and to sulfamethoxazole trimethoprim in 28.2%. In this regard, it is interesting to compare our data with results of a retrospective cohort study that included data from medical records of neonates infected by *E. coli* and hospitalized in NICU (USA, period 2009–2017, *n*=733). These results witnessed the highest levels of resistance to ampicillin (99.9%), aminoglycosides (99.7%), carbapenems (91.8%), cefazolin (95.8%), ceftriaxone (91.5%) and sulfamethoxazole trimethoprim (94.2%) [40]. Resistance of E. coli isolated from newborns in hospitals was demonstrated in the results of a multicenter study conducted in China (2021–2022): 75.5% of strains were resistant to cefotaxime, 65.4% to sulfamethoxazole trimethoprim, and 48.4% to ciprofloxacin [41]. The levels of *E. coli* resistance identified in our results are not as significant as in the studies cited above, but nevertheless indicate the risks of antibiotic therapy for neonatal infections caused by this pathogen.

Such MOs, as *A. baumanni* and *P. aeruginosa* were found in our study in 2.3 and 1.1%, respectively. According to the review by Pillay et al (2024), the frequency of NS caused by *A. baumannii* ranges from 1 to 6% [42]. Despite the fact that published data indicate a high level of resistance of this pathogen and the dominance of strains with multidrug resistance [43, 44], our study did not find similar results; the only ABDs to which a decrease in sensitivity was detected were cefepime (17% resistant) and sulfamethoxazole trimethoprim (6.3% resistant). *P. aeruginosa* is one of the MOs with the lowest frequency of detection in our work. In the practice of NICU work, this pathogen is not the leading one; however, its detection indicates the risk of a severe course of the infectious process and is associated with a high frequency of fatal outcomes. Among gram-negative causative agents of NS in Sweden (analysis of 11 years of practice), *P. aeruginosa* was detected in 3.7% of cases (4 out of 107), while resistance to ABDs was not detected [38]. Our data revealed variable levels of *P. aeruginosa* antibiotic resistance. 22.4% of strains were resistant to cefepime, 64.1% had intermediate resistance. Ceftazidime-resistant strains were seen in 30.5% and in 65.8% intermediate resistance was detected. Resistance to meropenem was identified in 20.1% and to amikacin in 19.5%.

### Limitations of the study

Our study included the materials of cultures of neonates hospitalized in the largest specialized clinic of the Russian Federation, however, these data may not reflect the landscape of pathogens typical for all regions of the country. Our study had retrospective design, and we did not assess the effectiveness of the antibiotic therapy. Also, the presented data did not include estimation of clinical outcomes depending on the type of pathogen identified and the parameters of its antibiotic resistance, which will be the next stage of our work.

## CONCLUSION

In the population of neonates hospitalized in the NICU with a mean gestational age of 34.6±4.8 weeks, we found a fairly high frequency of pathogen isolation — 39.3%. The largest number of pathogens was obtained from the pharynx (65.5%), rectum (10.4%) and endotracheal aspirate (8.9%). Gram-positive microflora dominated in the structure of pathogens (59.6%). Analysis of antibiotic resistance parameters revealed a high level of staphylococcal

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-378-393

resistance to oxacillin (71.2%). ESKAPE group MOs were determined in 28.6%, the leader was *S. aureus* (10.7%, of which 17% of strains were resistant to oxacillin). *K. pneumoniae* was the most common gram-negative MO (10.3%), almost half of the strains were resistant to ceftazidime (48.8%) and 100% — to ampicillin. *E. coli* was the second most frequently determined gram-negative MO identified in neonates in the NICU (9.2%). Resistance to ceftazidime was determined in 28.2% of strains, to ampicillin in 64.9%, and to sulfamethoxazole trimethoprim in 28.2%. *A. baumanni* and *Enterobacter* spp. were characterized by a fairly high sensitivity to all tested ABDs. For *P. aeruginosa*, minimal sensitivity was found to cefepime and ceftazidime (13.5 and 3.7%, respectively). Our results revealed an increase in the levels of antibiotic resistance of pathogens detected in NICU and indicate the importance of dynamic monitoring of the sensitivity of the microflora to the main ABDs used in NICU.

## FUNDING

This study did not have financial support from third-party organizations.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTON

Olga I. Butranova — idea, conducting of research, collection and analysis of data, writing and editing of the draft manuscript; Anastasiia A. Gorbacheva — data collection and analysis, editing of the draft manuscript; Sergey K. Zyryanov — critical revision of the draft manuscript, data collection and analysis of, approval of the final version of the draft manuscript; Oksana G. Ni — conducting of research, data collection and analysis. All authors made an equivalent and equal contribution to the preparation of the publication. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept and preparation of the article, read and approved the final version before publication)

## REFERENCES

1. Kulizhnikov GV, Furman EG, Nikolenko AV. Diagnostic value of laboratory markers of neonatal sepsis in premature infants. Pediatria n.a. G.N. Speransky. 2021;100(1):95–100. DOI: 10.24110/0031-403X-2021-100-1-95-100
2. Dmitriev AV, Zaplatnikov AL. Neonatal sepsis: modern diagnostic capabilities. Pediatria n.a. G.N. Speransky. 2022;101(1):140–8. DOI: 10.24110/0031-403X-2022-101-1-140-148
3. Flannery DD, Puopolo KM, Hansen NI, Sánchez PJ, Stoll BJ; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal infections: Insights from a multicenter longitudinal research collaborative. Semin Perinatol. 2022;46(7):151637. DOI: 10.1016/j.semperi.2022.151637
4. Moftian N, Samad Soltani T, Mirnia K, Esfandiari A, Tabib MS, Rezaei Hachesu P. Clinical Risk Factors for Early-Onset Sepsis in Neonates: An International Delphi Study. Iran J Med Sci. 2023;48(1):57–69. DOI: 10.30476/IJMS.2022.92284.2352
5. Sewell E, Roberts J, Mukhopadhyay S. Association of Infection in Neonates and Long-Term Neurodevelopmental Outcome. Clin Perinatol. 2021;48(2):251–61. DOI: 10.1016/j.clp.2021.03.001
6. Thomas R, Bijlsma MW, Gonçalves BP, Nakwa FL, Velaphi S, Heath PT. Long-term impact of serious neonatal bacterial infections on neurodevelopment. Clin Microbiol Infect. 2024;30(1):28–37. DOI: 10.1016/j.cmi.2023.04.017
7. Bedetti L, Corso L, Miselli F, Guidotti I, Toffoli C, Miglio R, Roversi MF, Muttini EDC, Pugliese M, Bertoncelli N, Zini T, Mazzotti S, Lugli L, Lucaccioni L, Berardi A. Neurodevelopmental Outcome after Culture-Proven or So-Called Culture-Negative Sepsis in Preterm Infants. J Clin Med. 2024;13(4):1140. DOI: 10.3390/jcm13041140
8. Odabasi IO, Bulbul A. Neonatal Sepsis. Sisli Etfal Hastan Tip Bul. 2020;54(2):142–58. DOI: 10.14744/SEMB.2020.00236
9. Guo L, Han W, Su Y, Wang N, Chen X, Ma J, Liang J, Hao L, Ren C. Perinatal risk factors for neonatal early-onset sepsis: a meta-analysis of observational studies. J Matern Fetal Neonatal Med. 2023;36(2):2259049. DOI: 10.1080/14767058.2023.2259049
10. Seyoum K, Sahiledengle B, Kene C, Geta G, Gomora D, Ejigu N, Mesfin T, Kumar Chattu V. Determinants of neonatal sepsis among neonates admitted to neonatal intensive care units in ethiopian hospitals: A systematic review and meta-analysis. Heliyon. 2023;9(9):e20336. DOI: 10.1016/j.heliyon.2023.e20336
11. Murthy S, Godinho MA, Guddattu V, Lewis LES, Nair NS. Risk factors of neonatal sepsis in India: A systematic review and meta-analysis. PLoS One. 2019;14(4):e0215683. DOI: 10.1371/journal.pone.0215683
12. Belachew A, Tewabe T. Neonatal sepsis and its association with birth weight and gestational age among admitted neonates in Ethiopia: systematic review and meta-analysis. BMC Pediatr. 2020;20(1):55. DOI: 10.1186/s12887-020-1949-x
13. Lloyd LG, Bekker A, Van Weissenbruch MM, Dramowski A. Healthcare-associated Infections in Very Low Birth-weight Infants in a South African Neonatal Unit: Disease Burden, Associated Factors and Short-term Outcomes. Pediatr Infect Dis J. 2022;41(11):911-6. DOI: 10.1097/INF.0000000000003666

14. Olenev AS, Konopliannikov AG, Songolova EN, Stetsyuk OV. Colonization of pregnant women with group B streptococcus: current view at the problem. Obstetrics, Gynecology and Reproduction. 2022;16(2):182–93. DOI: 10.17749/2313-7347/ob.gyn.rep.2022.284
15. Ferorelli D, Goffredo VM, Graziano E, Mastrapasqua M, Telegrafo M, Vinci A, Visci P, Benevento M, Zotti F, Foglianese A, Panza R, Solarino B, Dell'Erba A, Laforgia N. Quality improvement in neonatal care through enhanced patient safety and clinical risk management: a before-and-after study about neonatal sepsis. Front Med. 2024;11:1430853. DOI: 10.3389/fmed.2024.1430853
16. Karpova AL, Mostovoi AV, Martirosyan SV, Orlova OE, Karpov LN, Zaplatnikov AL. Early neonatal sepsis caused by *Haemophilus influenzae*. Obstetrics, Gynecology and Reproduction. 2023;17(3):366–75. DOI: 10.17749/2313-7347/ob.gyn.rep.2023.415
17. Glaser MA, Hughes LM, Jnah A, Newberry D. Neonatal Sepsis: A Review of Pathophysiology and Current Management Strategies. Adv Neonatal Care. 2021;21(1):49–60. DOI: 10.1097/ANC.0000000000000769
18. Pan T, Zhu Q, Li P, Hua J, Feng X. Late-onset neonatal sepsis in Suzhou, China. BMC Pediatr. 2020;20(1):261. DOI: 10.1186/s12887-020-02103-y
19. Tzialla C, Berardi A, Mondì V, On Behalf Of The Study Group Of Neonatal Infectious Diseases. Outbreaks in the Neonatal Intensive Care Unit: Description and Management. Trop Med Infect Dis. 2024;9(9):212. DOI: 10.3390/tropicalmed9090212
20. Parmigiani S, Bevilacqua G. Can we reduce worldwide neonatal mortality? Acta Biomed. 2022;93(5):e2022294. DOI: 10.23750/abm.v93i5.13225
21. Mahtab S, Madhi SA, Baillie VL, Els T, Thwala BN, Onyango D, Tippet-Barr BA, Akelo V, Igunza KA, Omore R, Arifeen SE, Gurley ES, Alam M, Chowdhury AI, Rahman A, Bassat Q, Mandomando I, Ajanovic S, Sitoe A, Varo R, Sow SO, Kotloff KL, Badji H, Tapia MD, Traore CB, Ogbuanu IU, Bunn J, Luke R, Sannoh S, Swarray-Deen A, Assefa N, Scott JAG, Madrid L, Marami D, Fentaw S, Diaz MH, Martines RB, Breiman RF, Madewell ZJ, Blau DM, Whitney CG; CHAMPS Consortium. Causes of death identified in neonates enrolled through Child Health and Mortality Prevention Surveillance (CHAMPS), December 2016 – December 2021. PLOS Glob Public Health. 2023;3(3):e0001612. DOI: 10.1371/journal.pgph.0001612
22. Jansen SJ, Lopriore E, van der Beek MT, Veldkamp KE, Steggerda SJ, Bekker V. The road to zero nosocomial infections in neonates-a narrative review. Acta Paediatr. 2021;110(8):2326–35. DOI: 10.1111/apa.15886
23. Cernada M, De Alba Romero C, Fernández-Colomer B, González-Pacheco N, González M, Couce ML; en representación del Comité de Estándares y la Comisión de Infección Neonatal de la Sociedad Española de Neonatología. Health care-associated infections in neonatology. An Pediatr (Engl Ed). 2024;100(1):46–56. DOI: 10.1016/j.anpede.2023.12.004
24. Huang J, Cayabyab R, Cielo M, Ramanathan R. Incidence, Risk Factors, Short-term Outcomes, and Microbiome of Ventilator-associated Pneumonia in Very-low-birth-weight Infants: Experience at a Single Level III Neonatal Intensive Care Unit. Pediatr Infect Dis J. 2024. DOI: 10.1097/INF.0000000000004440
25. Prochaska EC, Xiao S, Colantuoni E, Clark RH, Johnson J, Mukhopadhyay S, Kalu IC, Zerr DM, Reich PJ, Roberts J, Flannery DD, Milstone AM; CDC Prevention Epicenters Program. Hospital-Onset Bacteremia Among Neonatal Intensive Care Unit Patients. JAMA Pediatr. 2024;178(8):792–9. DOI: 10.1001/jamapediatrics.2024.1840
26. Oldendorff F, Nordberg V, Giske CG, Navér L. A decade of neonatal sepsis in Stockholm, Sweden: Gram-positive pathogens were four times as common as Gram-negatives. Eur J Clin Microbiol Infect Dis. 2024;43(5):959–68. DOI: 10.1007/s10096-024-04809-8
27. Sorsa A. Epidemiology of Neonatal Sepsis and Associated Factors Implicated: Observational Study at Neonatal Intensive Care Unit of Arsi University Teaching and Referral Hospital, South East Ethiopia. Ethiop J Health Sci. 2019;29(3):333–42. DOI: 10.4314/ejhs.v29i3.5
28. Guo J, Luo Y, Wu Y, Lai W, Mu X. Clinical Characteristic and Pathogen Spectrum of Neonatal Sepsis in Guangzhou City from June 2011 to June 2017. Med Sci Monit. 2019;25:2296–304. DOI: 10.12659/MSM.912375
29. Wang J, Zhang H, Yan J, Zhang T. Literature review on the distribution characteristics and antimicrobial resistance of bacterial pathogens in neonatal sepsis. J Matern Fetal Neonatal Med. 2022;35(5):861–70. DOI: 10.1080/14767058.2020.1732342
30. Song WS, Park HW, Oh MY, Jo JY, Kim CY, Lee JJ, Jung E, Lee BS, Kim KS, Kim EA. Neonatal sepsis-causing bacterial pathogens and outcome of trends of their antimicrobial susceptibility a 20-year period at a neonatal intensive care unit. Clin Exp Pediatr. 2022;65(7):350–7. DOI: 10.3345/cep.2021.00668
31. Marchant EA, Boyce GK, Sadarangani M, Lavoie PM. Neonatal Sepsis Due to Coagulase-Negative Staphylococci. Clin. Dev. Immunol. 2013;2013:586076. DOI: 10.1155/2013/586076
32. Le KY, Villaruz AE, Zheng Y, He L, Fisher EL, Nguyen TH, Ho TV, Yeh AJ, Joo HS, Cheung GYC, Otto M. Role of Phenol-Soluble Modulins in *Staphylococcus epidermidis* Biofilm Formation and Infection of Indwelling Medical Devices. J. Mol. Biol. 2019;431:3015–27. DOI: 10.1016/j.jmb.2019.03.030
33. Ferreira ICDS, Menezes RP, Jesus TA, Lopes MSM, Araújo LB, Ferreira DMLM, Röder DVDB. Oxacillin-resistant *Staphylococcus spp.*: Impacts on fatality in a NICU in Brazil – confronting the perfect storm. Biomed Pharmacother. 2024;179:117373. DOI: 10.1016/j.biopha.2024.117373
34. Magnan C, Morsli M, Salipante F, Thiry B, Attar JE, Maio MD, Safaria M, Tran TA, Dunyach-Remy C, Ory J, Richaud-Morel B, Sotto A, Pantel A, Lavigne JP. Emergence of multidrug-resistant *Staphylococcus haemolyticus* in neonatal intensive care unit in Southern France, a genomic study. Emerg Microbes Infect. 2024;13(1):2353291. DOI: 10.1080/22221751.2024.2353291
35. Westberg R, Stegger M, Söderquist B. Molecular Epidemiology of Neonatal-Associated *Staphylococcus haemolyticus* Reveals Endemic Outbreak. Microbiol Spectr. 2022;10(6):e0245222. DOI: 10.1128/spectrum.02452-22
36. Shadbolt R, We MLS, Kohan R, Porter M, Athalye-Jape G, Nathan E, Shrestha D, Strunk T. Neonatal *Staphylococcus aureus* Sepsis: a 20-year Western Australian experience. J Perinatol. 2022;42(11):1440–5. DOI: 10.1038/s41372-022-01440-3

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-6-378-393

37. Wang L, Zhen JH, Dong F, Lyu ZY. Cross-sectional Hospital-based Investigation on Clinical Characteristics of Pediatric *Staphylococcus aureus* Isolates in a Beijing Hospital from 2013 to 2022. Infect Drug Resist. 2024;17:4899–912. DOI: 10.2147/IDR.S486832
38. Nordberg V, Iversen A, Tidell A, Ininbergs K, Giske CG, Navér L. A decade of neonatal sepsis caused by gram-negative bacilli-a retrospective matched cohort study. Eur J Clin Microbiol Infect Dis. 2021;40(9):1803–13. DOI: 10.1007/s10096-021-04211-8
39. You T, Zhang H, Guo L, Ling KR, Hu XY, Li LQ. Differences in clinical characteristics of early- and late-onset neonatal sepsis caused by *Klebsiella pneumoniae*. Int J Immunopathol Pharmacol. 2020;34:2058738420950586. DOI: 10.1177/2058738420950586
40. Flannery DD, Akinboyo IC, Mukhopadhyay S, Tribble AC, Song L, Chen F, Li Y, Gerber JS, Puopolo KM. Antibiotic Susceptibility of *Escherichia coli* Among Infants Admitted to Neonatal Intensive Care Units Across the US From 2009 to 2017. JAMA Pediatr. 2021;175(2):168–75. DOI: 10.1001/jamapediatrics.2020.4719
41. Guo Y, Xiao R, Feng J, Wang X, Lai J, Kang W, Li Y, Zhu X, Ji T, Huang X, Pang D, An Y, Meng L, Wang Y. Distribution of virulence genes and antimicrobial resistance of Escherichia coli isolated from hospitalized neonates: A multi-center study across China. Heliyon. 2024;10(16):e35991. DOI: 10.1016/j.heliyon.2024.e35991
42. Pillay K, Ray-Chaudhuri A, O'Brien S, Heath P, Sharland M. *Acinetobacter spp.* in neonatal sepsis: an urgent global threat. Front Antibiot. 2024;3:1448071. DOI: 10.3389/frabi.2024.1448071
43. Elvan Tüz A, Tekin D, Ekemen Keleş Y, Şahin A, Üstündağ G, Taşar S, Kara Aksay A, Karadağ Öncel E, Yılmaz D. Clinical Reflections of *Acinetobacter* Infections in Children in a Quaternary-Care Hospital: A Five-Year Single-Center Experience. Turk Arch Pediatr. 2024;59(1):38–42. DOI: 10.5152/TurkArchPediatr.2024.23153
44. Mohamed RAE, Moustafa NM, Mahmoud FM, Elsaadawy YS, Aziz HSA, Gaber SAB, Hussin AM, Seadawy MG. Whole-genome sequencing of two multidrug-resistant *Acinetobacter baumannii* strains isolated from a neonatal intensive care unit in Egypt: a prospective cross-sectional study. BMC Microbiol. 2024;24(1):362. DOI: 10.1186/s12866-024-03482-3

## AUTHORS

**Olga I. Butranova** – Candidate of Sciences (Medicine), Assistant Professor of the Department of General and Clinical Pharmacology of the Medical Institute, Peoples' Friendship University (RUDN University). ORCID ID: 0000-0001-7729-2169. E-mail: butranova-oi@rudn.ru

**Anastasiia A. Gorbacheva** – Assistant Lecturer of the Department of General and Clinical Pharmacology of the Medical Institute, Peoples' Friendship University (RUDN University); врач-клинический фармаколог Kommunarka Center (Moscow, Russia). ORCID ID: 0009-0003-9721-6931. E-mail: gorbacheva_aa@pfur.ru

**Sergey K. Zyryanov** – Doctor of Sciences (Medicine), Professor, Head of the Department of General and Clinical Pharmacology of the Peoples' Friendship University (RUDN University); Deputy Chief Physician of the City Clinical Hospital No. 24 (Moscow, Russia). ORCID ID: 0000-0002-6348-6867. E-mail: zyryanov_sk@rudn.university

**Oksana G. Ni** – Head of the Department of Clinical Pharmacology of the Kommunarka Center (Moscow, Russia). ORCID ID: 0000-0003-0994-0579. E-mail: ni.oksana@gmail.com