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PROGNOSIS AND EFFECTIVENESS OF ANTIBACTERIAL TREATMENT OF ENDOMETRITIS AFTER CESARIAN SECTION WITH ISOLATING DRUG-RESISTENT ESKAPE PATHOGENS

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♦ **Purpose.** The purpose of this study was to determine the frequency of isolation of drug-resistant ESKAPE pathogens isolation in endometritis after cesarean section; to assess the prognosis of the disease and the effectiveness of initial empirical antimicrobial therapy for isolating multiresistant pathogens.

Methods. A retrospective analysis of all the cases of endometritis after cesarean section in St. Petersburg was performed. The study period: September 2008 – September 2019.

Results. 68 (26.7%) out of 255 cases of endometritis after cesarean section were caused by pathogens of the rESKAPE group. In puerperas with endometritis caused by rESKAPE pathogens, the following are more often observed: clinical failures in prescribing initial empirical antimicrobial therapy compared with endometritis of another etiology ($p = 0.0012$); severe course of infectious process with the risk of its generalization and hysterectomy ($p < 0.05$).

Conclusions. Endometritis after abdominal delivery caused by rESKAPE pathogens is associated with an unfavorable prognosis of the disease and a high risk of ineffective antimicrobial therapy.

♦ **Keywords:** endometritis after cesarean section; cesarean delivery; drug-resistant ESKAPE pathogens.

ПРОГНОЗ И ЭФФЕКТИВНОСТЬ ЭТИОТРОПНОГО ЛЕЧЕНИЯ ЭНДОМЕТРИТА ПОСЛЕ КЕСАРЕВА СЕЧЕНИЯ ПРИ ИЗОЛЯЦИИ ВОЗБУДИТЕЛЕЙ ГРУППЫ ESKAPE

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♦ **Цель** — определение частоты изоляции лекарственно устойчивых ESKAPE-патогенов (rESKAPE) при эндометрите после кесарева сечения, оценка прогноза заболевания и результатов стартовой эмпирической антимикробной терапии при изоляции полирезистентных возбудителей.

Методы. Проведен ретроспективный анализ всех случаев эндометрита после кесарева сечения в Санкт-Петербурге. Период исследования: сентябрь 2008 — сентябрь 2019 г.

Основные результаты. Из 255 случаев эндометрита после кесарева сечения 68 (26,7 %) были обусловлены патогенами группы rESKAPE. У родильниц с эндометритом, вызванным rESKAPE-патогенами, чаще отмечены клинические неудачи при назначении стартовой эмпирической антимикробной терапии, чем при эндометрите другой этиологии ($p = 0,0012$); тяжелое течение инфекционного процесса с угрозой его генерализации и гистерэктомией ($p < 0,05$).

Закключение. Эндометрит после абдоминального родоразрешения, вызванный rESKAPE-патогенами, связан с неблагоприятным прогнозом заболевания и высоким риском отсутствия эффекта от антимикробной терапии.

♦ **Ключевые слова:** эндометрит после кесарева сечения; полирезистентные возбудители; ESKAPE-патогены.

Introduction

Although infections caused by multidrug-resistant ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae* и *Escherichia coli*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter spp.*) have recently been recognized globally as a major health problem [1–3], their role in the development of postpartum infection is still unknown. To date, trials on the targeted study of infections caused by resistant ESKAPE (rESKAPE) pathogens are limited and, as a rule, based on data from patients admitted in intensive care units [4, 5]. Studies conducted in different countries have shown that infections caused by rESKAPE pathogens are associated with higher mortality, an increase in the duration of hospital stay, and an increase in treatment costs [2].

This study aimed to determine the frequency of isolation of rESKAPE pathogens in endometritis after cesarean section (CS) to assess disease prognosis and results of initial empirical antimicrobial therapy in the presence of multidrug-resistant pathogens.

Materials and methods

A retrospective observational multicenter study was performed. The main clinical bases were St. Petersburg City Mariinsky Hospital and maternity hospitals in St. Petersburg. The study was conducted in the period from September 2008 to September 2019, during which 225 puerperas hospitalized with a diagnosis of endometritis after CS were examined and treated in the gynecological department of the City Mariinsky Hospital.

All postpartum women were distributed into two groups, namely, those with endometritis caused by rESKAPE pathogens and those with endometritis caused by susceptible ESKAPE strains. To assess the prognosis and efficacy of empiric antimicrobial therapy for endometritis after CS caused by rESKAPE pathogens, an intergroup comparison was performed.

Pathogens of the rESKAPE group are designated according to the descriptions in the literature [1–5]. Resistance to rESKAPE pathogens was identified if the following strains were identified: vancomycin-resistant *E. faecium* (VRE), methicillin-resistant *S. aureus* strains (MRSA), *K. pneumoniae* and *E. coli* producing extended

spectrum β -lactamases (ESBL+), carbapenem-resistant *A. baumannii* (Carb-R), carbapenem- and quinolone-resistant *P. aeruginosa*, and ESBL-producing *Enterobacter* strains.

Bacteria were identified using conventional methods of culture diagnostics and confirmed using mass spectrometry. The susceptibility of *S. aureus* oxacillin was tested on a disk with cefoxitin (30 μ g). The presence of MRSA was confirmed by the results of a multi-primer polymerase chain reaction (PCR). For gram-negative bacteria, ESBL was confirmed using a combined synergistic test with two disks with and without cefotaxime, ceftazidime, and clavulanic acid. In vitro, the susceptibility of ESBL isolates was determined on an automatic analyzer Vitek using AST-N156 cards (bioMérieux, Marcy-L'Etoile, France) with interpretive control points. The susceptibility of *Enterococcus spp.* to vancomycin was determined on a Vitek analyzer (AST-P586 cards), and the presence of *van* genes encoding glycopeptide resistance was detected using multi-primer PCR. Moderately resistant and resistant pathogens were combined into a group of insensitive strains.

The values of quantitative indicators were compared using the Mann–Whitney test for the nonparametric analysis of the indicators. The chi-square test was used to evaluate differences in qualitative parameters. The relationship between the characteristics of the endometritis course and the presence of antibiotic-resistant strains of endometritis pathogens were identified using correlation analysis by calculating Spearman's correlation coefficient, which was used for indicators with nonnormal distribution. Differences were considered statistically significant when the threshold value of the statistical significance level of the null hypothesis ($\alpha = 0.05$) was not reached.

Results

During the study period, 68 of 225 (26.7%) cases of endometritis after CS caused by rESKAPE pathogens were verified. None of these infections indicated any nosocomial outbreak in the obstetric hospitals under study. Two or more bacteria were not isolated simultaneously in the multidrug-resistant rESKAPE group. Figure 1 shows the number of rESKAPE isolates in comparison with their antibiotic-sensitive counterparts.

Among isolated multidrug-resistant rESKAPE pathogens, the number of gram-negative pathogens was higher (57 of 68 cases, 83.8%) than that of gram-positive pathogens (11 of 68 cases, 16.2%).

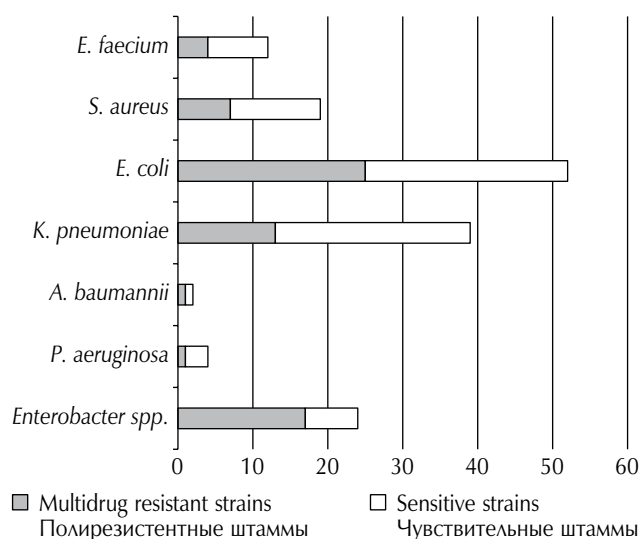
E. coli ranks first, affecting 25 of 68 (36.8%) cases, with endometritis caused by rESKAPE pathogens. Nearly half of isolated *E. coli* (25 of 52 cases, 48.1%) were ESBL producers. In every fourth case of endometritis caused by rESKAPE pathogens, that is, in 17 of 68 (25.0%) cases, multidrug-resistant strains of the *Enterobacter* genus (*E. cloacae* and *E. aerogenes*) of the *Enterobacteriaceae* family were detected. Few susceptible strains of *Enterobacter* were identified, with 7 of 24 cases (29.2%).

The involvement of *K. pneumoniae* in the development of puerperal infection is becoming an urgent problem due to the increased etiological significance and worsening of their phenotype of resistance to antibiotics used. Our data revealed that multidrug-resistant *Klebsiella* is isolated less frequently than *E. coli*, but their incidence was comparable with the incidence of *Enterobacter spp.* *Klebsiella spp.* (ESBL+) accounted for one-third of all isolated *Klebsiella* strains.

VRE accounted for 33.3% (4 of 12 cases), methicillin-sensitive *S. aureus* accounted for 63.2% (12 of 19 cases), and MRSA accounted for 36.8% (7 of 19 cases) of their corresponding total cases.

Non-fermenting gram-negative rESKAPE bacteria were identified with an extremely low frequency. Therefore, Carb-R and carbapenem- and quinolone-resistant *P. aeruginosa* are not substantial in the etiology of endometritis after CS.

Thus, in addition to a large group of the most well-known pathogens of postoperative infection in puerperas who underwent CS, the significance of multidrug-resistant rESKAPE pathogens increases.



Sensitivity of isolates to antimicrobial agents in endometritis after cesarean section (absolute number)

Чувствительность выделенных изолятов к антимикробным препаратам при эндометрите после кесарева сечения (абсолютное количество штаммов)

The mean time of clinical manifestation of postoperative endometritis was shorter during the isolation of rESKAPE pathogens than those of diseases caused by other microorganisms (3.1 ± 0.7 versus 4.9 ± 1.1 days, $p < 0.05$) (Table 1). The average duration of hospital stay was longer in puerperas with endometritis caused by rESKAPE pathogens (14.9 ± 3.5 and 9.1 ± 2.2 days, $p = 0.0006$).

Severe symptoms of a systemic inflammatory reaction with generalized infection were noted more often in patients with endometritis caused by rESKAPE than those endometritis with caused by unidentified rESKAPE pathogens, i.e., in 17 cases (25.0%) versus 12 cases (6.4%) ($p = 0.0012$). Moreover, in this group, the treatment was statistically significantly more often ineffective than with the group of patients with

Table 1 / Таблица 1

The timing of the clinical manifestation of postoperative endometritis and the duration of inpatient treatment, $M \pm m$
Сроки клинической манифестации послеоперационного эндометрита и длительность стационарного лечения, $M \pm m$

Indicators	Patients with endometritis with unidentified rESKAPE pathogens, $n = 187$	Patients with endometritis with identified rESKAPE pathogens, $n = 68$
Timing of clinical manifestation of postoperative endometritis, days	4.9 ± 1.1	$3.1 \pm 0.7^*$
Duration of hospital stay, days	9.1 ± 2.2	$14.9 \pm 3.5^*$

Note. * differences are statistically significant at $p < 0.05$ compared with those of patients in whom rESKAPE pathogens were not identified (Mann-Whitney test).

Table 2 / Таблица

The indicators of the effectiveness of treating endometritis after cesarean section, $M \pm m$ Показатели эффективности лечения послеоперационного эндометрита, $M \pm m$

Indicators	Patients with endometritis with identified rESKAPE pathogens, $n = 68$		Patients with endometritis with unidentified rESKAPE pathogens, $n = 187$	
	n	%	n	%
Generalized infection	17	25.0	12	6.4*
Treatment failure	24	35.3	27	14.4*

Note. * differences are statistically significant at $p < 0.05$ compared with those of patients with identified rESKAPE pathogens (chi-square test).

Table 3 / Таблица 3

The effect of multiresistant pathogens on the clinical course of endometritis after cesarean section and the effectiveness of etiotropic treatment

Влияние полирезистентных возбудителей на клиническое течение эндометрита после кесарева сечения и эффективность этиотропного лечения

Factor	Spearman's correlation coefficient	p index
Total duration of etiotropic treatment	0.377	0.017
Change in antimicrobial chemotherapy drug	0.434	0.0012
Transfer to an observational hospital (no effect of conservative treatment in the maternity hospital)	0.521	<0.001
Generalized infection	0.537	0.022
Hysterectomy	0.428	0.0009
Duration of hospital stay	0.461	<0.001

endometritis of a different etiology, i.e., 24 cases (35.3%) versus 27 cases (14.4%) ($p = 0.008$) (Table 2).

Thus, in puerperas with endometritis caused by rESKAPE pathogens, a more severe course of infection and clinical failures in prescription of initial empirical antimicrobial therapy were more often recorded.

The correlation analysis of the clinical course and results of treatment of puerperas with isolation of rESKAPE pathogens from metaspirates showed that the presence of multi-resistant strains of endometritis pathogens is a significant predictor of an unfavorable course and poor disease prognosis. Table 3 shows direct statistically significant moderate correlations between the isolation of multidrug-resistant pathogens and factors such as the duration of etiotropic treatment ($R = 0.377$; $p = 0.017$), frequency of changing the antimicrobial chemotherapy drug ($R = 0.434$; $p = 0.0012$), number of transfers to an observational hospital ($R = 0.521$; $p < 0.001$), frequency of generalized infection ($R = 0.537$; $p = 0.022$), frequency of

hysterectomy ($R = 0.428$; $p < 0.001$), and duration of hospital stay ($R = 0.461$; $p < 0.001$).

The data obtained indicate that the antibiotic resistance of pathogens deteriorates the results of treatment and thereby increases the duration of antibacterial treatment and hospital stay.

Discussion

This retrospective multicenter study of puerperas with endometritis after CS represents a regional analysis of the epidemiological characteristics and prognosis of postoperative infectious and inflammatory complications in obstetrics associated with rESKAPE infection, as well as the effect of inadequate prescription of standard antibiotics in this cohort of patients on treatment efficacy.

Among the investigated rESKAPE microorganisms, isolates of *Klebsiella*, *Enterobacter*, and *Serratia*, which are ESBL producers, were the most common. These pathogenic microorganisms serve increasingly more often as causative agents of infections that develop during medical

care, and they are associated with a poor prognosis [6]. Only two cases of *K. pneumoniae* strains producing carbapenemases were identified in the present study, in contrast to other studies where these pathogens were more common and caused difficulties in treatment [10].

In the development of endometritis after abdominal delivery, we detected four vancomycin-resistant *E. faecium* strains and seven MRSA strains. Thus, these gram-positive cocci are less of a problem than gram-negative rods of the *Enterobacteriaceae* family, at least in St. Petersburg. Other authors cited higher rates of MRSA in obstetric patients [7].

The structure of enterobacteria isolated from puerperas with endometritis is varied, of which *E. coli* is predominant (found in every third puerperant). Half of them were producers of extended spectrum β -lactamases.

Considering the high kinetic significance of *E. coli* in the occurrence of postpartum infection in maternity hospitals, in our opinion, this microorganism should also be included in the ESKAPE pathogen group. Nevertheless, according to a number of studies, the epidemiology and risk factors for contamination with this infection differ from those in other ESBL-producing *Enterobacteriaceae*, such as *K. pneumoniae* (ESBL+) [8]. Although the incidence of horizontal transmission of *K. pneumoniae* (ESBL+) during hospital stay is high, horizontal transmission of *E. coli* (ESBL+) is probably low [9].

Adequate antibiotic treatment is of utmost importance. However, a small number of antimicrobial drugs are currently available for the treatment of infections caused by multidrug-resistant microorganisms. Given the near-complete absence of *P. aeruginosa* (Carb-R) and *A. baumannii* (Carb-R) strains in the puerperas enrolled in our study, carbapenems preferred drugs for infections caused by ESBL-producing *Enterobacteriaceae* microorganisms. Colistin or some aminoglycosides can be used as second-line drugs, but these antibiotics are contraindicated during lactation.

Analysis of the results of the initial empirical etiotropic treatment of women with endometritis after CS revealed that the isolation of rESKAPE pathogens is a risk factor for an unfavorable disease course and prognosis. Multidrug resistance of pathogens deteriorates the results of an antimicrobial therapy, increases the duration of stay in

the obstetric hospital, and aggravates the disease prognosis.

Statistically significant correlations were found between the probability of isolating rESKAPE as endometritis causative agents and the severity of infection that led to generalization and hysterectomy.

Conclusion

The study results demonstrated that endometritis after abdominal delivery due to rESKAPE pathogens causes an unfavorable prognosis, a high risk of inefficiency of antimicrobial therapy, and risk for surgical treatment (hysterectomy). Therefore, from the perspective of nosocomial epidemiology, further monitoring of the main and secondary risk factors for the occurrence of multi-resistant rESKAPE pathogens is necessary for the stratification of pregnant women and puerperas. Such effort will help in the utilization of effective measures to prevent and treat post-operative infection and inflammation.

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