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Predicting peritoneal contamination with enterobacteria producing extended-spectrum beta-lactamases and choosing empirical antibacterial therapy for postoperative peritonitis in cancer patients

Relevance: Enterobacteriaceae family microorganisms, specifically *E. coli* and *K. pneumoniae* isolates, are the most common activators of postoperative peritonitis in oncology. Many of these microorganisms produce extended-spectrum beta-lactamases (ESBL). The deemed resistance of ESBL-producing enterobacteria to all β -lactam antibiotics, except for carbapenems, leads to the ineffectiveness of empiric antibiotic therapy.

The purpose of the study was to define the risk factors of peritoneal contamination with ESBL-producing enterobacteria for choosing optimal empirical antibacterial therapy on the example of a specific cancer patient with postoperative peritonitis.

Results: Independent risk factors of peritoneal contamination with ESBL-producing enterobacteria included "the administration of antibiotics for more than three days" (OR 106, 95% CI 21.0-537, $p < 0.001$), "two or more repeated laparotomies" (OR 2.66, 95% CI 1.32-5.34, $p = 0.006$), and "postoperative preventive antibiotic treatment" (OR 0.17, 95% CI 0.04-0.75, $p = 0.02$). The obtained prognostic model allowed predicting the infection with ESBL-producing enterobacteria before establishing the postoperative peritonitis microbial etiology. The model sensitivity was 94.7%, overall predictive accuracy was 73.1.

Conclusion: Prolonged administration of antibiotics (3rd-generation cephalosporins and/or fluoroquinolones) after cancer surgery to prevent surgical infections is the main independent risk factor of peritoneal contamination with ESBL-producing enterobacteria.

Keywords: cancer patients, postoperative peritonitis, extended-spectrum beta-lactamases (ESBL)-producing enterobacteria, empirical antibacterial therapy (ABT), carbapenems.

Introduction: Postoperative peritonitis (PP) in cancer patients is difficult to treat and leads to high mortality (up to 37% and more). Moreover, inadequate antibiotic therapy (ABT) is associated with significantly higher mortality [1]. The main reason for ABT failure is the nosocomial bacterial strains' resistance to antibiotics. Adequate ABT for PP, especially the one caused by multidrug-resistant (MDR) microorganisms such as enterobacteria producing extended-spectrum β -lactamases (ESBL), is not an easy task. Identifying risk factors for MDR bacteria improves the adequacy of empirical ABT in PP [2], and antifungal prophylaxis is efficient for patients at high risk of candidemia after major abdominal surgeries [3]. An evidence-based approach to the administration of ABT is required not only since microorganisms of the enterobacteria family, including isolates of *E. coli* and *K. pneumoniae*, are the most frequent causative agents of secondary peritonitis in oncology but also due to a higher level of bacterial resistance to antibiotics often used in PP compared with peritonitis not associated with oncological surgery [4].

The purpose of the study was to define the risk factors of peritoneal contamination with ESBL-producing enterobacteria for choosing optimal empirical antibacterial therapy on the example of a specific cancer patient with postoperative peritonitis.

Materials and Methods: The study involved 303 cancer patients with PP treated at the N.N. Alexandrov Republican Scientific and Practical Centre of Oncology and Radiology

(Minsk, Belarus) in 2008-2013. All patients have developed microbiologically confirmed peritonitis after abdominal oncological surgery.

The identification of microorganisms and the determination of their sensitivity to antibiotics was carried out using Vitek-2 Compact 60 and Vitek-2 Compact 30 automatic analyzers (BioMérieux, France). The phenotypes of ESBL-producing enterobacteria were determined and confirmed using ESBL ETEST cards (BioMérieux) and antibiograms.

The influence of various prognostic factors on the risk of infection with ESBL-producers was assessed by the logistic regression method using direct stepwise regression based on Wald statistics. Before entering data, patients were divided into two groups. The first group included 109 (36%) patients with isolates of ESBL-producing *K. pneumoniae* and/or *E. coli*, identified at least once as part of a mono-infection or in combination with other microorganisms. The second group included 194 (64%) patients with the pathogens of peritonitis presented by other aerobic microorganisms such as *K. pneumoniae* and *E. coli* that do not produce ESBL. Variables considered as risk factors included unambiguously interpreted qualitative and quantitative predictors. The two groups of patients were compared using the χ^2 test and Fisher's exact test, considering the acceptance conditions. Odds ratios (OR) were calculated with a 95% confidence interval (CI). A p -value < 0.05 was considered statistically significant. Individual predic-

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tors included in the multivariate logistic regression model had the p -value < 0.1 .

Internal model validation was performed using a bootstrap. The degree of correspondence of the predicted probability to the observed ESBL-producer frequency was assessed by constructing a calibration graph; the accuracy of the prediction model was assessed by the area under the ROC curve (AUC).

The mathematical model was developed using the SPSS v.22.0 program (SPSS Inc., Chicago, IL, USA).

Results:

The direct stepwise regression analysis included 29 factors ($n = 29$) characterizing the patient and the treatment given; their significance in univariate analysis was determined. We selected 9 factors having a significant ($p < 0.05$) effect and 2 factors having a close to significant ($p < 0.1$) effect on the risk of infection with ESBL-producing enterobacteria. These are such predictors as: surgery on the proximal parts of the gastrointestinal tract ($p = 0.027$); urological and/or gynecological surgery ($p = 0.031$); pre-

operative ABT ($p = 0.044$); postoperative ABT ($p < 0.001$); antibiotic prophylaxis (ABP) with fluoroquinolones (FQ) ($p < 0.001$); the use of antibiotics such as 3rd-generation cephalosporins (CP) or FQ for 3 days or more after elective surgery ($p < 0.001$); stay in the ICU for more than 1 day ($p = 0.012$); two relaparotomies or more ($p = 0.002$); hollow organ defect detected though relaparotomy ($p = 0.006$); serous or serofibrinous peritonitis ($p = 0.053$); fibro-purulent peritonitis ($p = 0.063$). All of them ($n = 11$) are included in the multivariate logistic regression model (multivariate analysis).

The final mathematical model contained three independent risk factors for ESBL-producing enterobacteria. Those factors reflected the use of antibiotics for therapeutic and prophylactic purposes before repeated laparotomy and the effectiveness of surgical treatment of peritonitis (Table 1). Independent factors related to resistant enterobacteria included: "antibiotics for 3 days or more" ($p < 0.001$), "two repeated laparotomies or more" ($p = 0.006$), and "postoperative ABP" ($p = 0.02$).

Table 1 – Final model of logistic regression for the equation variables ($n = 3$)

Final predictors	Regression parameters					
	B	SE	Wald	P	exp (β)	95% CI for exp (β)
Postoperative ABP	-1.800	0.771	5.450	0.020	0.165	0.036–0.749
Two relaparotomies or more	0.977	0.357	7.497	0.006	2.656	1.320–5.343
Antibiotics for 3 days or more	4.664	0.825	31.932	<0.001	106.06	21.038–534.678
Constant	-2.958	0.486	36.987	<0.001	0.052	-

Note: β -values used to calculate the threshold level are highlighted in grey

The β and exp (β) values in the equation (Table 1) show that "antibiotics for three days or more" (OR 106; 95% CI 21.0–535; $p < 0.001$) had the maximum effect on the dependent variable; the rate of "two or more repeated laparotomies" (OR 2.66; 95% CI 1.32–5.34; $p = 0.006$) had a much smaller effect. The third predictor, "postoperative blood pressure" (OR 0.17, 95% CI 0.04–0.75; $p = 0.02$), reduced the likelihood of resistant bacteria.

The cut-off value was 0.36 since ESBL-producing enterobacteria caused 36% of the observed cases of peritonitis. The threshold linear predictor value was -0.853. Therefore, the $p(ESBL+)$ index above -0.853 indicated the peritoneum infection with ESBL-producing enterobacteria; the $p(ESBL+)$ below -0.853 meant the absence of that pathogen.

The obtained mathematical model of β -values lead to Formula 1:

$$p(BLRS+) = -2,958 + 4,664 \times AB + 3cyT + 0,977 \times REL - 1,8 \times POABP \quad (1)$$

Where, $p(BLRS+)$ – the rate of infection with ESBL-producers;

AB > 3 days – a systemic administration of antibiotics ("administration of antibiotics for three days or more" was equal to 1, "administration of antibiotics for less than three days" or "only preoperative ABP" was equal to 0);

REL – repeated laparotomy ("two repeated laparotomies or more" were equal to 1, "one repeated laparotomy" or "no repeated operation" were equal to 0);

POABP – postoperative ABP (the positive answer was equal to 1, the negative – to 0).

Substituting the values into the model equation (1), we got the following: in the presence of three or two predictors, one of which was the factor with the greatest impact ("antibiotics for three days or more") or in the presence of that predictor only we could predict the peritoneum infection with ESBL-producing enterobacteria.

The resulting prediction model allowed predicting the infection caused by ESBL-producing enterobacteria with a sensitivity of 94.7% before the microbial etiology of peritonitis would be established. The overall forecast accuracy was 73.1% (Table 2).

During internal validation performed using bootstrap, the ROC AUC showed the adequacy of the developed model in addition to the prediction dots (Figure 1).

Table 2 – Prediction of the infection with ESBL-producing enterobacteria (cut-off value – 0.36)

Observed			Predicted		
			ESBL+		Correctly predicted (%)
			No	Yes	
Step 1	ESBL+	No	108	68	61.4
		Yes	5	90	94.7
	Total percent				73.1

Figure 1 – ROC-curve of the method for predicting the peritoneum infection with ESBL-producing enterobacteria

Figure 2 – Calibration graph for predicting the infection with ESBL-producing enterobacteria

The ROC analysis showed high informative value of the resulting model: AUC=0.832, 95% CI 0.786-0.879; $p < 0.001$.

The constructed calibration graph (Figure 2) showed a high correspondence of the predicted probability to the observed frequency of the peritoneum infection with ESBL producers.

Discussion: β -lactamases' production is one of the most common and clinically significant mechanisms of resistance of gram-negative bacteria [5]. ESBL – enzymes that hydrolyze penicillins, aztreonam, and CS; ESBL-producing enterobacteria are considered resistant to all β -lactam antibiotics except carbapenems. With the widespread prevalence of ESBL-producing enterobacteria, especially in patients with nosocomial intra-abdominal infection (IAI) (20.6-42.8%) [6], carbapenems are the drugs of choice for empirical ABT [6, 7]. The re-

cent emergence of carbapenemases and metallo- β -lactamases suggests even greater problems for clinicians [8-11] since they are resistant to all β -lactam antibiotics, including carbapenems.

According to the regression analysis, the peritoneum infection with ESBL-producing enterobacteria was not associated with most of the variables characterizing the patient and cancer treatment. Only a few predictors related to reoperation data (nature of exudate, hollow organ defect, number of reoperations) were indirectly associated with resistant enterobacteria. The main influence was due to the use of antibiotics in preoperative and postoperative periods, which determined "antibiotics for three days or more" as a factor with the greatest influence. Similar data in assessing risk factors for ESBL-producing bacteria in patients with complicated

IAI were shown in a Thailand study [12]. Initially, three predictors, including nosocomial IAI, previous hospitalization, and previous use of antibiotics (CS and β -lactamase inhibitors), were associated with ESBL-producing infections; however, multivariate analysis showed that only nosocomial origin of infection (OR 5.26; 95% CI 1.07–25.9; $p = 0.041$) was an independent risk factor for IAI caused by ESBL producers. The relationship between the previous antibiotic treatment and a high proportion of ESBL producers was also confirmed in a multicenter study CIAOW [6].

Algorithm of carbapenem administration: Evaluation of surgical component of treatment for complicated IAI is paramount for disease outcome since it is unlikely that ABT will be efficient if control of the source of infection is not radical [13]. The leading role of surgical treatment in the outcome of PP is also characteristic

for cancer patients [1]. Therefore, the radicalism of sanitizing surgery should be considered when prescribing empirical ABT. The proposed prediction model urges the use of carbapenem group antibiotics in the started or restarted therapy of PP even if the patient does not have a predictor that has a maximum impact on the dependent variable – prolonged (more than three days) use of antibiotics after planned oncological surgery. Probably, there is no need for carbapenems or other broad-spectrum drugs only provided radical sanitation of the infection foci and in the absence of all three risk factors.

Thus, the developed prediction model suggests the following algorithm of empirical use of carbapenems considering the quality of surgical sanitation of the abdominal cavity and the elimination of the source for infection (Figure 3):

Risk factor		Surgical sanitation	
		Radical	Non-radical
Antibiotics (CS III or FQ) for 3 days or more after planned oncological surgery	No	No	Yes
	Yes	Yes/no	Yes

Yes – carbapenem is prescribed, no – carbapenem is not prescribed

Figure 3 – Indications for empirical use of carbapenems in postoperative peritonitis in cancer patients

Conclusions: The prolonged use of antibiotics (3rd-generation CS and/or FQ) to prevent surgical infections after planned oncological surgeries is the main independent risk factor for the peritoneum infection with ESBL-producing enterobacteria.

The most associated factor with the risk of peritoneum infection with ESBL-producing enterobacteria could be prevented in most cases. This requires the adherence to one of the postulates of modern preoperative ABP: limiting the use of antibiotics to the duration of the intervention or to a short time (no more than 24 hours) after a planned surgery.

References:

1. Shishlo I. F. *Tipichnye abdominal'nye onkologicheskie operacii i ishod posleoperacionnogo peritonita* [Typical abdominal oncological operations and the outcome of postoperative peritonitis] // *Novosti xirurgii* [News of Surgery]. – 2010. – № 6 (18). – P. 66–74;
2. Augustin P., Kermarrec N., Muller-Serieys C., Lasocki S., Chosidow D., Marmuse J-P., Valin N., Desmonts J-M., Montravers Ph. Risk factors for multidrug resistant bacteria and optimization of empirical antibiotic therapy in postoperative peritonitis // *Crit. Care*. – 2010. – Vol. 14, № 1. – P. 20–27. DOI: 10.1186/cc8877;
3. Kilic A. U., Basaga S. M., Cevahir F., Cakir O., Doganay M., Alp E. Risk prediction for candidemia in surgical intensive care unit patients // *North Clin. Istanbul*. – 2020. – Vol. 7, №4. – P. 348–353. doi: 10.14744/nci.2020.27136;

4. Shishlo I. F. *E'tiologicheskaya struktura vtorichnogo peritonita i chuvstvitel'nost' kishechnoj palochki k antibiotikam u onkologicheskix bol'nyx* [Etiological structure of secondary peritonitis and sensitivity of *E. coli* to antibiotics in cancer patients] // *Onkol. Zh.* [Cancer J.]. – 2010. – T. 4, № 1 (13). – S. 84–88;

5. Nicasio A.M., Kuti J.L., Nicolau D.P. The current state of multidrug-resistant gram-negative bacilli in North America // *Pharmacother.* – 2008. – Vol. 28, №2. – P. 235–249. DOI: 10.1592/phco.28.2.235;

6. Sartelli M., Catena F., Ansaloni L. et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study // *World J. Emerg. Surg.* – 2014. – Vol. 9: 37. DOI: 10.1186/1749-7922-9-37;

7. Malloy A.M.W., Campos J.M. Extended-spectrum beta-lactamases: a brief clinical update // *Pediatr. Infect. Dis. J.* – 2011. – Vol. 30, №12. – P. 1092–1103. DOI: 10.1097/INF.0b013e31823c0e9d;

8. Vardakas K.Z., Tansarli G.S., Petros I., Rafailidis P.I., Falagas M.E. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β -lactamases: a systematic review and meta-analysis // *J. Antimicrob. Chemother.* – 2012. – Vol. 67. – P. 2793–2803. DOI: 10.1093/jac/dks301;

9. Bush K. Bench-to-bedside review: The role of β -lactamases in antibiotic-resistant Gram-negative infections // *Crit. Care*. – 2010. – Vol. 14, №3. – P. 224. DOI: 10.1186/cc8892;

10. Dmitrieva N.V., Aginova V.V., Petuxova I.N., Grigor'evskaya Z.V., Dmitrieva A.I., Bagirova N.S., Tereshhenko I.V., Xmaladze E.N. *Nosokomial'nye infekcii, vyzvannye bakteriyami semeystva Enterobacteriaceae, v onkologicheskoy klinike* [Nosocomial infections

caused by bacteria of the Enterobacteriaceae family in oncological clinical practice] // *Sib. Onkol. Zh. [Sib. Oncol. J.]*. – 2019. – Vol. 18, №1 – P. 36–42. DOI: 10.21294/1814-4861-2019-18-1-36-42;

11. Lim F.K., Liew Y.X., Cai Y., Lee W., Teo J.Q.M., Lay W.Q., Chung J., Kwa A.L.H. Treatment and Outcomes of Infections Caused by Diverse Carbapenemase-Producing Carbapenem-Resistant Enterobacterales // *Front Cell Infect. Microbiol.* – 2020. – Vol. 10. – 579462. DOI: 10.3389/fcimb.2020.579462;

12. Boontham P., Soontomrak R. Intra-Abdominal Infections: Prevalence and Risk Factors of ESBLs Infections // *J. Med. Assoc. Thai.* – 2015. – Vol. 98, №11. – P. 1097–1103;

13. Solomkin J. S., Ristagno R. L., Das A. F., Cone J. B., Wilson S. E., Rotstein O. D., Murphy B. S., Severin K. S., Bruss J. B. Source control review in clinical trials of anti-infective agents in complicated intra-abdominal infections // *Clin. Infect. Dis.* – 2013. – Vol. 56, №12. – P. 1765–1773. DOI: 10.1093/cid/cit128.

ТҰЖЫРЫМ

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Ішпердеге кеңейтілген спектрлі β-лактамазаларды бөлетін энтеробактериялардың жұққанын болжау және онкологиялық науқастарда операциядан кейінгі перитонит үшін эмпирикалық антибиотикалық терапияны таңдау

Өзектілігі: Энтеробактериялар тұқымдасының микроорганизмдері, негізінен *E. coli* және *K. pneumoniae* изоляттары, онкологияда операциядан кейінгі перитонит (ПП) қоздырғыштары болып табылады. Олардың арасында кеңейтілген спектрлі β-лактамазаларды (КСБЛ) өндіретін бактериялардың кең таралуын ескере отырып, эмпирикалық антибиотикалық терапияның (АБТ) тиімсіздігіне байланысты сұрақтар жиі туындайды, өйткені КСБЛ өндіретін энтеробактериялар карбапенемдерден басқа, барлық β-лактамады антибиотиктерге (АБ) төзімді болып саналады.

Зерттеудің мақсаты - ПП-мен ауыратын белгілі бір онкологиялық науқастарда эмпирикалық АБТ-нің оңтайлы режимін таңдау үшін, ішперге *E. coli* және *K. pneumoniae* өндіретін кеңейтілген спектрлі β-лактамазаларды (КСБЛ) жұғу қауіпі факторларын анықтау.

Нәтижелер: Ішпердеге КСБЛ-ды өндіретін энтеробактериялардың жұғуының тәуелсіз қауіп факторлары: «3 күннен артық АБ» (ОШ 106; 95% ДИ 21,0–535; $p < 0.001$), «екі немесе одан да көп релапаротомия» (ОШ 2,66; 95% ДИ 1,32–5,34; $p = 0.006$) және «операциядан кейінгі антибиотикалық профилактика» (ОШ 0,17; 95% ДИ 0,04–0,75; $p = 0.02$) сияқты өзгермелі факторлар болып табылады. Алынған модель ПП микробтық этиологиясын орнатпас бұрын, 94,7% сезімталдығымен КСБЛ-ды өндіретін энтеробактериялар тудыратын инфекцияның болуын болжауға мүмкіндік береді. Жалпы болжамның дәлдігі 73,1% құрады.

Қорытынды: іш қуысына КСБЛ-ды өндіретін энтеробактериялардың жұғуының негізгі тәуелсіз факторы - хирургиялық инфекциялардың алдын алу мақсатында қатерлі ісік операциясынан кейін антибиотиктерді (үшінші буын цефалоспорины және/немесе фторхинолоны) ұзақ уақыт қолдану болып табылады.

Түйінді сөздер: онкологиялық науқастар; операциядан кейінгі перитонит; кеңейтілген спектрлі β-лактамазалар шығаратын энтеробактериялар; эмпирикалық антибиотикалық терапия; карбапенемдер.

АННОТАЦИЯ

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Прогнозирование инфицирования брюшины энтеробактериями, продуцирующими β-лактамазы расширенного спектра, и выбор эмпирической антибактериальной терапии послеоперационного перитонита у онкологических пациентов

Актуальность: Микроорганизмы семейства энтеробактерий, в основном изоляты *E. coli* и *K. pneumoniae*, являются наиболее частыми возбудителями послеоперационного перитонита (ПП) в онкологии. В условиях широкой распространенности среди них бактерий, продуцирующих β-лактамазы расширенного спектра (БЛРС), часто возникают вопросы, связанные с неэффективностью эмпирической антибактериальной терапии (АБТ), поскольку энтеробактерии, вырабатывающие БЛРС, считаются устойчивыми ко всем β-лактамам антибиотикам (АБ), кроме карбапенемов.

Цель исследования – определить факторы риска инфицирования брюшины БЛРС-продуцентами *E. coli* и *K. pneumoniae* для выбора оптимального режима эмпирической АБТ у конкретного онкологического пациента с ПП.

Результаты: Независимыми факторами риска инфицирования брюшины энтеробактериями-продуцентами БЛРС оказались такие переменные, как: «антибиотики в течение более 3 суток» (ОШ 106; 95% ДИ 21,0–535; $p < 0.001$), «две и более релапаротомии» (ОШ 2,66; 95% ДИ 1,32–5,34; $p = 0.006$) и «послеоперационная антибиотикопрофилактика» (ОШ 0,17; 95% ДИ 0,04–0,75; $p = 0.02$). Полученная модель прогнозирования дает возможность, до установления микробной этиологии ПП, с чувствительностью 94,7% предсказать наличие инфекции, вызванной БЛРС-продуцентными энтеробактериями. Общая точность прогноза составила 73,1%.

Заключение: Основным независимым фактором риска инфицирования брюшной полости энтеробактериями, продуцирующими БЛРС, является продолжительное использование антибиотиков (цефалоспоринов III поколения и/или фторхинолонов) после онкологической операции с целью профилактики хирургических инфекций.

Ключевые слова: онкологические пациенты; послеоперационный перитонит; энтеробактерии, продуцирующие β-лактамазы расширенного спектра; эмпирическая антибактериальная терапия; карбапенемы.