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PREVALENCE OF EXTENDED SPECTRUM BETA LACTAMASE PRODUCING BACTERIA IN TWO SURGICAL WARDS OF A GENERAL HOSPITAL

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Colonisation of gastrointestinal tract by extended spectrum beta lactamase (ESBL)-producing Gram-negative bacteria is a source for infections. The present work is a prospective study in Latvia aimed to determine the role of two surgical profile wards in transmission of ESBL-producing bacteria. Differences between hospital wards were not analysed due to low number of patients. We have also determined a correlation between the duration of hospitalisation and risk of ESBL colonisation. Tests for ESBL-producing bacteria were made twice for 136 patients — upon admission and upon discharge from the hospital. Of them, 21 (15.4%) patients already were ESBL-positive at the time of admission and 115 (84.6%) patients were ESBL-negative. Upon discharge from hospital, 45 (33.1%) patients were ESBL-positive, one patient was ESBL-negative, and 25 (18.4%) of ESBL-positive cases had emerged during hospitalisation. In total, 46 (33.8%) from 136 patients were ESBL-positive and ESBL was positive in 51 bacterial isolates. On discharge from hospital, the newly acquired ESBL-positive bacterial isolates were K. pneumoniae *(n = 18),* E. coli *(n = 7) and* P. mirabilis *(n = 3). The prevalence of ESBL-positive* E. coli *from all detected* E. coli *was 7.0% and from all* Klebsiella *spp. — 88.9% in gut flora. Analysis of patient-associated wound infections did not show correlation between the ESBL-producing gut microbiota and the bacterial species involved in wound infection.*

Key words: *ESBL, bacterial colonisation, gut microbiota.*

INTRODUCTION

Extended spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria have been a major cause of hospital-acquired infections since the mid-1980s (Paterson and Bonomo, 2005) and thus the main reason for the clinical use of broad spectrum antibiotics, including cephalosporins and monobactams (Knothe *et al.,* 1983; Hoffmann *et al.,* 2006; Paberza *et al*., 2007).

Infections caused by ESBL-producing microorganisms vary from urinary tract infections to severe sepsis, with the most typical representatives of *Enterobacteriaceae* family involved (Deepti and Deepti, 2010). This taxonomic group includes *Escherichia coli, Klebsiella pneumoniae* and *Enterobacter cloacae*. Other authors mention *Proteus mirabilis* (Cohen-Nahum *et al.,* 2010). These bacteria can be found in nosocomial settings and also in the community (Zahar *et al.,* 2015). The major risk factors for infection with ESBL-producing microorganisms include prolonged hospital stay, antibacterial therapy, invasive procedures, severe comorbidities, immunosuppression and intra-abdominal surgery (Asir *et al.,* 2015).

According to the European Center of Disease Control Surveillance 2013 report, in Latvia approximately 50% of *K. pneumoniae* and 10–25% of *E. coli* are ESBL producers (Anonymous, 2013).

ESBL-producing bacteria associated with infections in Latvia are found most frequently in the digestive tract system (Skuja *et al.,* 2015). However, the presence of ESBL-producing bacteria in gut microbiota in the hospital has been poorly studied in Latvia. The risk of being infected by

resistant microbiota or to acquire ESBL-producing bacteria as a part of gut microbiota during hospitalisation has not been evaluated yet.

The aim of the present study was to determine the frequency of ESBL-producing bacteria among the *Enterobacteriaceae* in patients at two Latvian surgical profile wards of Rīga East University on admission and on discharge. One of the wards specialises in soft tissue infections including diabetic foot and the other in the treatment of burns. We determined correlation between the acquisition of ESBL bacteria and duration of stay in hospital; therefore, we determined the prevalence of ESBL in faeces for patients both at admission and at discharge from hospital. Also, we aimed to analyse the etiological spectrum of surgical site infections (SSI) and its correlation to ESBL prevalence in gut.

MATERIALS AND METHODS

The retrospective study was conducted at Rīga East University Hospital (REUH). All ESBL-producing bacteria isolates were obtained from the Rīga East University Hospital Bacteriology Laboratory starting from November 2015. The study was coordinated by the University of Latvia and approved by the Scientific Research Ethics Commission of the Institute of Experimental and Clinical Medicine, University of Latvia.

Clinical and microbiological data were recorded for 136 patients admitted into surgical and burn wards, from whom faecal and wound samples were collected. Culture isolates were obtained from patient gut microbiota at admission and on discharge from the hospital. Bacterial samples were collected using swabs from wounds and rectum.

A VITEK® 2 automated system (Biomerieux, France) was used for microbial identification (Spanu *et al*., 2003). All 136 bacterial isolates were screened for the presence of ESBL-producing bacteria using the double disk diffusion method and determination of minimum inhibitory concentration (MIC) method (for *P. mirabilis*) according to Clinical and Laboratory Standards Institute (CLSI- 2017-M100-S27). The ceftazidime and cefotaxime double disk method is a standard marker used for determination of ESBL-producing bacteria (Jarlier *et al*., 1998). For bacterial susceptibility testing, the disk diffusion method with the following antibacterial disks was used: cefotaxime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg), gentamicin (10 µg), amikacin (30 µg), ampicillin (10 µg), ciprofloxacin (5 µg), levofloxacin (10 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), meropenem (10 µg) and imipenem (10 µg).

RESULTS

ESBL-producing bacteria were collected twice from 136 patients — upon admission and on discharge from the hospital. In total, 46 (33.8%) from 136 patients were ESBL positive and ESBL was found to be positive for 51 bacterial isolates.

The duration of ESBL-positive inpatient stay was from 1 to 47 days; on average patients spent 11 days at the hospital, with modal value 6 days. The largest number of patients (14) spent 6–10 days in the hospital (Fig. 1). There were nine newly acquired ESBL-positive patients. Six patients spent from one to five days at the hospital, another ten patients spent approximately two weeks at the hospital, and four patients had a longer duration of hospitalisation — more than 25 days. Twenty-five of the 136 patients were ESBL-positive and repeatedly hospitalised.

In order to show the risk of acquiring ESBL-producing bacteria in gut microbiota due to hospitalisation, we compared ESBL-positive microbiota versus ESBL-negative microbiota on the day of the admission to the hospital and on the day of the discharge. Our results showed negative tendency for ESBL colonisation. Twenty-one (15.4%) of 136 patients were ESBL positive on admission, and 115 (84.6%) were ESBL negative at admission. Twenty-five patients had gained ESBL-positive microbiota by the time of discharge from hospital; therefore, in total, 45 patients were ESBL-positive on discharge from the hospital (Table 1). This group indicates the increased risk of acquiring ESBL-producing bacteria during a stay in closed environment. Interestingly, one patient was ESBL-positive upon admission in a hospital, but negative on discharge from hospital, indicating loss of ESBL-producing bacteria from the intestinal tract.

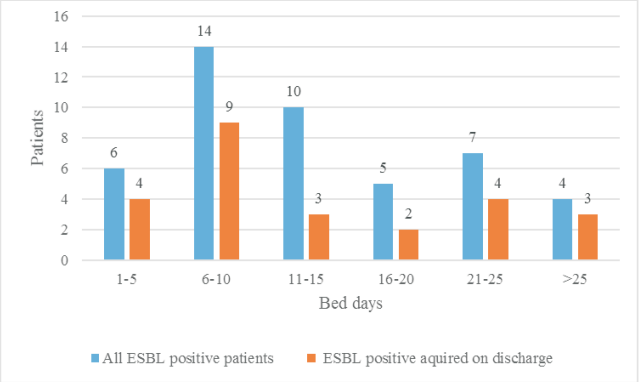

Fig. *1*. Number of patients with extended spectrum beta lactamase (ESBL)-positive species regarding the hospitalisation duration.

Table 1

NUMBER OF PATIENTS WITH ESBL-POSITIVE AND NEGATIVE GUT MICROBIOTA AT ADMISSION AND ON DISCHARGE FROM HOSPITAL, SHOWN IN NUMBERS AND IN PERCENTAGE

	At admission (total n = 136)	On discharge (total n = 136)
ESBL Positive	n = 21* (15.4%)	n = 45 (33.1%)
ESBL Negative	n = 115 (84.6%)	n = 91 (66.9%)

*Including one patient who was ESBL-positive at admission and became ESBL-negative by the day of discharge from hospital.

Table 2

PATIENTS COLONISED WITH ESBL-POSITIVE AND NEGATIVE GUT MICROBIOTA AT ADMISSION AND ON DISCHARGE FROM HOSPITAL

	ESBL-positive			ESBL-negative		
Name of bacteria	*K. pneumoniae*	*E. coli*	*P. mirabilis*	*K. pneumoniae*	*E. coli*	*P. mirabilis*
At admission	6 (22.2%)	12 (8.8%)	5 (62.5%)	18 (75.0%)	7 (38.9%)	3 (37.5%)
On discharge*	24 (88.9%)	18(13.2%)	8 (100.0%)	0 (0%)	1(5.6%)	0 (0%)

*Including one patient who was ESBL-positive at admission and was ESBL-negative on the day of discharge from hospital.

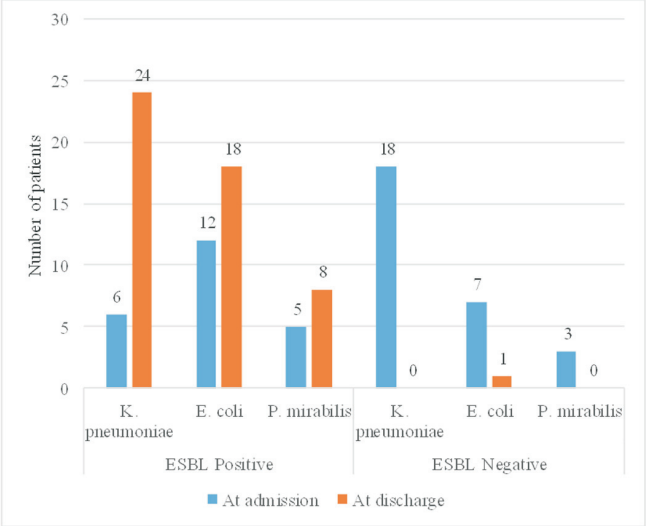

Fig. 2. Number of patients with ESBL-positive and negative gut microbiota at admission and on discharge from the hospital.

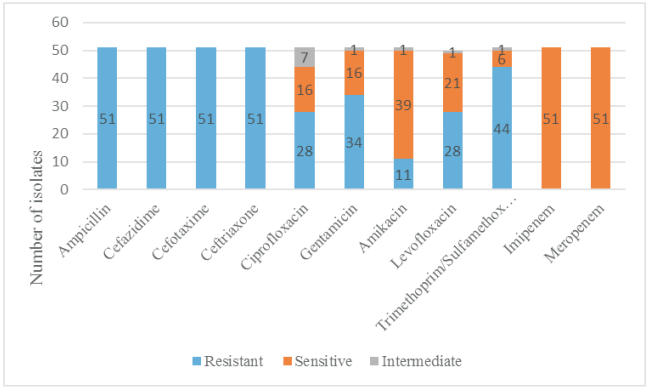

Fig. 3. Antimicrobial susceptibility of ESBL-positive *Enterobacteriaceae* family bacterial isolates from gut microbiota, shown as antibiograms.

Representatives of three genera of *Enterobacteriaceae* family, namely, *Klebsiella*, *Escherichia* and *Proteus*, were identified and tested for ESBL production. On discharge from hospital, *K. pneumoniae* (n = 24) was the most frequently isolated ESBL-producing bacteria species from 51 ESBL-positive isolates (faecal samples), followed by *E. coli* (n = 19;) and *P. mirabilis* (n = 8) (Table 2, Fig. 2). Polymicrobial flora was detected in five (9.8%) isolates. There was an increase in frequency of *K. pneumoniae* from 22.2% to 88.9% between admission and on discharge from hospital. Also, the number of cases of ESBL-positive P. mirabilis and *E. coli* increased on discharge from hospital, respectively, 100.0% and 13.2%.

All bacterial isolates were tested for antibacterial susceptibility by conventional susceptibility testing. Antimicrobial susceptibility of ESBL-positive *Enterobacteriaceae* family bacteria is shown in Figure 3. Antibiograms showed that all tested bacteria were susceptible to carbapenems (meropenem and imipenem), but were completely resistant to cephalosporins (100.0%). Also, most of the bacterial isolates exhibited resistance to trimethoprim-sulfamethoxazole (n = 44; 86.3%) and to gentamicin (n = 34; 66.7%). In seven cases (13.7%) susceptibility to ciprofloxacin was evaluated as intermediate, as shown in Figure 3.

Mostly representatives of *Enterobacteriaceae* family were identified among those isolated from gut and wound infections. Of the ESBL-positive bacteria, the most frequent were *E. coli* (n = 19; 7.0%), *K. pneumoniae* (n = 24; 47.1%), followed by *P. mirabilis* (n = 8; 5.0%). The proportion of these species was lower in wounds — *K. pneumoniae* (n = 1; 1.9%), *E. coli* and *P. mirabilis* (n = 2; 3.7%). No ESBL positive isolates were identified in wound infections.

No methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococci* species were found in gut microbiota. However, coagulase-negative staphylococci (CoNS) were predominant (n = 10; 18.5%) in wound microbiota, followed by *Pseudomonas aeruginosa* (n = 6; 11.1%) and MRSA (n = 2; 3.7%).

Wound infection was diagnosed in 26 (58.7%) of 46 ESBL patients. The most commonly isolated bacteria from wound infections were *S. aureus* (n = 8, 23.7%), CoNS (n = 6, 15.8%) and methicillin-resistant *Staphylococcus aureus* (MRSA) (n = 5, 13.2%). Ten (n = 10, 26.9%) bacterial isolates belonged to polymicrobial microbiota, including *S. aureus,* MRSA, CoNS, *P. aeruginosa* etc. In this group, only two species of the *Enterobacteriaceae* family (*P. mirabilis* and *K. pneumonia*) were identified. None of them were identified as ESBL-producing bacteria, as shown in Figure 4.

For inpatients with ESBL-producing bacteria, the main reasons of hospitalisation were burns, frostbites, bedsores, and type 2 diabetes mellitus with complications such as diabetic foot and gangrene. Diabetic foot infection was diagnosed in eight cases. Surgeries were performed on 13 patients during the hospitalisation period. Twenty-five of the patients had to be re-admitted due to complications (data not shown).

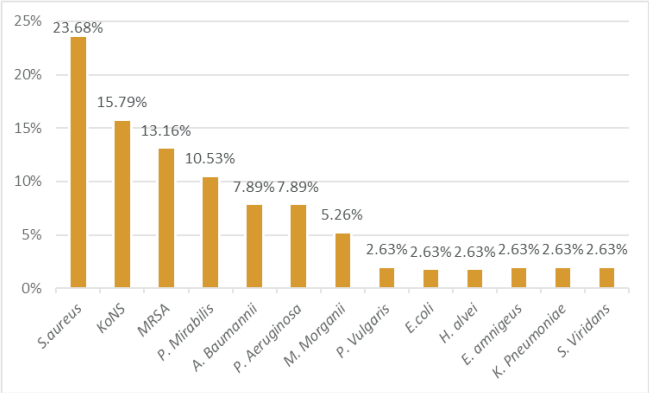

Fig. 4. Percentage of patients with bacterial isolates.

The most common bacterial species detected in wounds of ESBL-positive patients were *S. aureus* (n = 9; 23.7%), CoNS (n = 6; 15.8%), MRSA (n = 5; 13.2%), *P. mirabilis* (n = 4; 10.5%), *A. baumannii* (n = 3; 7.9%), *P. aeruginosa* (n = 3; 7.9%), and *M. morganii* (n = 2; 5.3%). Bacterial species, isolated only once were as follows: *P. vulgaris, E. coli, H. alvei, E. amnigenus, K. pneumoniae* and *S. viridans* (n = 1; 2.6%). ESBL-producing Gram-negative bacteria were found only in gut microbiota, not in the wound isolates.

DISCUSSION

The digestive tract plays a crucial role in the development of antibacterial resistance through selection and multiplication of resistant bacteria in hospitals and in the community. It is also a place where exchange of resistance genes occurs and selection of resistant bacteria due to antibacterial treatments plays an important role (Carlet, 2012). Since the 1980s, after introduction of cephalosporines in clinical practice, ESBL producers were discovered among *Klebsiella* spp. and *Enterobacter* spp. ESBL were encoded by the mutated genes of the plasmid-borne bla_{TEM} and bla_{SHV} wild-type penicillinase genes (Kliebe *et al.,* 1985; Petit *et al.,* 1990). Apart from hospital-acquired infections, ESBL are present in non-outbreak situations, also in the community.

Despite the global dissemination of ESBL-producing bacteria *Enterobacteriaceae* (ESBL-E), there is a lack of guidelines on screening and isolation protocols of ESBL-E carriers in hospitals. Primary screening for ESBL bacteria colonisation is used for intensive care unit (ICU) patients, because of higher rates of outbreaks than in other wards (Woerther *et al*., 2013).

Previous studies on the prevalence of ESBL-E in hospitalised patients in Latvia are limited (Paberza *et al*., 2007). In that study of Paberza *et al*., the prevalence of ESBL-producing *Klebsiella* and *E. coli* was 37.7% and 6.0%, respectively, in gut microbiota. This differs from our study, as the respective prevalence was 88.8% and 13.2% in gut microbiota. To our knowledge, our study is the first attempt in Latvia to screen hospitalised patients for ESBL-producing bacteria in gut microbiota. The screening was done only for three months, so that data to be comparable to other countries. From these results it is clear that there is urgent need for further screening of patients for ESBL, to determine if the prevalence and tendency is tending to increase or decrease.

In our study 33.8 % (n = 46) of the studied patients were carried ESBL microbiota in the gastrointestinal tract. In comparison, in Europe the highest rate 11.6% was observed in Belgium in a geriatric unit (Schoevaerdts *et al*., 2012).

The review by Woerther *et al*. (2013) shows that transmission of ESBL microbiota in Europe has increased from 2002 to 2011. The highest prevalence rates in the world have been reported from South-East Asia and China, where they reached nearly 70% in 2013 (Reuland *et al.*, 2016).

Our hypothesis was that the longer time a patient spends in the hospital, the greater is risk to gain a colonisation by gut ESBL. According to our data, nine of 14 (64.0%) patients who spent six to ten days at the hospital, gained ESBL-positive flora, and three of four patients who spent more than 25 days in hospital were positive. Our hypothesis was confirmed, as the duration of hospitalisation increased the risk of gaining ESBL-positive gut microbiota.

The largest group of nine patients had ESBL-producing microbiota, being the highest prevalence among other groups.

Comparing our results to other studies, where average duration of hospitalisation from the date of admission to date of a positive culture for ESBL-producing bacteria was 25 days with mean hospital stay 47 days, according to Rubio-Perez *et al*. 2012. In a study by Shaihk *et al*. (2015), mean duration of hospital stay was 5.63 days among patients gaining ESBL-producing bacteria, and a period of three days of hospital stay was found to be a significant risk factor for obtaining ESBL-producing bacteria. We cannot compare these results to our study, since duration of hospitalisation was different. However, it does appear that an increase in hospitalisation time longer than three days stay multiplies the risk for colonisation with ESBL microbiota. This was the limitation of our study, since patients did not stay in the hospital for more than on average 14 days, due to specificity of wards, etc. surgery and burns. Further studies are needed to find association between a longer period of stay in the hospital and ESBL-E carriage. Our study shows that relatively more ESBL-E-producing bacteria were detected, which might be explained by antimicrobial selection. It is known from other studies that ESBL bacteria carriers have a longer length of stay in the hospital due to an ESBL-E-producing bacterial infection or comorbidity (Willemsen *et al.*, 2015).

Interestingly, *S. aureus* 23.7% and CoNS 15.8% from patient wounds were found to be the predominant ESBL-producing bacteria. This finding differs from previous studies, where, according to the ECDC Surveillance 2013 report data, more than 50% of *K. pneumoniae* and 10–25% of *E. coli* clinically significant strains in Latvia produced ESBL (Hawser *et al.,* 2010; Skuja *et al.,* 2015).

According to data from the European Antimicrobial Resistance Surveillance System (EARSS), 2.6% of *E. coli* and 1.7% of *K. pneumoniae* strains in Sweden were resistant to third-generation cephalosporins in 2010 (Sibhghatulla *et al*., 2015). The percentage of isolates that express resistance to third-generation of cephalosporins was found to be lowest in Sweden (3.0%), Norway (3.6%) and Finland (5.1%) and highest in Bulgaria (22.9%), Slovakia (31.0%) and Cyprus (36.2%). *E. coli* strains resistant to fluoroquinolones were present in low numbers in Sweden (7.9%), Norway (9.0%) and Estonia (9.9%) while they were predominant in Italy (40.5%), Slovakia (41.9%) and Cyprus (47.4%) (Allocati *et al.,* 2013).

We were also interested to determine a correlation between the carriage of ESBL-producing bacteria in gut microbiota and the prevalence of those in wound infection. Another clinical study in Latvia showed that *K. pneumoniae* was mostly isolated from wounds (48.5%) and was the most frequently isolated ESBL-producing bacteria in all clinical cases (Skuja *et al.,* 2015).

It is known that wound infections caused by bacteria are most often associated with prolonged hospital stay and thus subsequent risk of acquiring multiple resistant organisms from medical devices and hospital environment (Idowu *et al*., 2011).

Therefore, in our study the clinical material from wounds (namely, pus) was investigated in 26 patients and identified by culturing. However, none of the identified bacterial species from wounds were characterised as ESBL-producing bacteria.

Notably, our results for most frequently isolated species, namely, *S. aureus* 23.7% and CoNS 15.8%, revealed to be different from those of other studies, where *Klebsiella* species (88.88%) were the most common ESBL producers from the skin wound infections, *E. coli* (61.5%) and *Pseudomonas* species (100.0%) (Yasmin *et al*., 2015).

The difference in the prevalence of ESBL-positive bacteria in wounds in our study compared to other studies can be explained by the relatively small number of ESBL-positive patients (n = 46) in our study. Our results indicate that there is no risk for ESBL-positive bacteria in wounds, but further studies are required. Evaluation of the data on ESBL prevalence in gut microbiota indicates that repeated hospitalisation is an important risk factor for gaining ESBL-E by a patient. There is an obvious need for molecular characterisation of ESBL-producing genes (CTX. TEM and SHV plasmid groups) encoded by plasmids (Caratolli, 2009; Canton *et al.,* 2012; Liakopoulos *et al*., 2016).

Data on faecal carriage with ESBLs in healthy individuals are lacking for most countries, but the rate has been estimated to be 10% in Asia and 5.5% in Spain. The geographical differences in the prevalence of ESBL microbiota in clinical cultures extend in proportion with healthy individuals colonised with ESBL-producing isolates (Tängdén *et al.,* 2010).

To our knowledge, no previous research has been made on the prevalence of ESBL-E carriage in the Latvian population, but this could be an additional source of resistant bacteria spread and the risk for patients during hospitalisation. As an example, our previous studies of methicillin resistant *S. epidermidis* in the community showed that the prevalence of resistant species was 12.5% in the nasal cavity of healthy persons (Līduma 2016). The study of Mulki and co-authors (Mulki *et al.,* 2017) showed that patients are likely to spread high loads of ESBL-producing bacteria in the environment. Additionally, in future studies it would be important to evaluate additional risk factors for gaining ESBL carriage, e.g., repeated hospitalisation or transfer, previous antibiotic treatment and catheterisation. This would provide better understanding on ESBL gain and spread risk factors in Latvian hospitals.

CONCLUSIONS

1. The inpatient colonisation with ESBL-producing bacteria is relatively high in Latvia.

2. The hospital environment is a promoting factor for ESBL prevalence in patients.

3. No correlation was found between the wound infection and gut colonisation with ESBL-producing *Enterobacteriaceae.*

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PLAŠA SPEKTRA BETA LAKTAMĀŽU PRODUCĒJOŠO BAKTĒRIJU KOLONIZĀCIJA DIVĀS SLIMNĪCAS ĶIRURĢISKAJĀS NODAĻĀS

Plaša spektra beta laktamāžu (PSBL) producējošo baktēriju kolonizācija zarnu traktā ir dažādu infekciju avots. Šis ir pirmais prospektīvais pētījums Latvijā, kura mērķis bija vērtēt divu ķirurģiskā profila nodaļu nozīmi PSBL producējošo gramnegatīvo baktēriju pārnesē. Atšķirības starp slimnīcas nodaļām netika analizētas nelielā pacientu skaita dēļ. Mūsu pētījuma otrs mērķis bija noteikt korelāciju starp pacientu hospitalizācijas ilgumu un iegūto zarnu mikrofloru. PSBL producējošās baktērijas 136 pacientiem tika izmeklētas divas reizes — iestājoties un izrakstoties no slimnīcas. Iestājoties slimnīcā, 21 (15,4%) pacientam jau bija PSBL producējoši zarnu izolāti un 115 (84,6%) pacientiem bija PSBL negatīvi. Izstājoties no slimnīcas, 45 (33,1%) pacienti bija PSBL pozitīvi, bet viens pacients bija PSBL negatīvs, turpretim 25 (18,4%) pacientiem tā bija parādījusies no jauna hospitalizācijas laikā. Kopumā pētījuma laikā 46 (33,8%) no 136 pacientiem bija atrasta PSBL pozitīva flora, un konstatēts, ka PSBL pozitīvs bija 51 baktēriju izolāts. Izrakstoties no slimnīcas, jauniegūtie baktēriju izolāti tika atrasti *K. pneumoniae* (n = 18), *E. coli* (n = 7) un *P. mirabilis* (n = 3). No visām izolētajām *E. coli* baktērijām PSBL pozitīvu *E. coli* prevalence abās slimnīcas nodaļas bija 7,0% un *Klebsiella* — 88,9% zarnu mikroflorā. Analizējot PSBL pacientu pavadošas brūču infekcijas, korelācija starp PSBL kolonizāciju zarnu traktā un infekciju etioloģiju netika atrasta.