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DECREASING PREVALENCE OF MULTIDRUG-RESISTANT *ACINETOBACTER BAUMANNII* IN RĪGA EAST UNIVERSITY HOSPITAL

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There has been an increasing tendency of infections caused by multidrug-resistant organisms (MDRO), including multidrug-resistant Acinetobacter baumannii (MDRAB), in the Rīga East University Hospital (REUH) during the last decade. Over the last two years (2014–2015), this tendency has reversed and the prevalence of MDRAB has decreased considerably. In this study we assessed the prevalence of MDRAB in intensive care units (ICUs), internal medicine, surgery units and analysed antibiotic sensitivity profiles. In addition, we determined if current infection control measures are preventing further increase of infections caused by MDRAB in REUH.

Retrospective Acinetobacter baumannii *prevalence data were collected for the period from 2009 until 2012. For the time period from the beginning of 2013 until 2015, after implementing such infection control measures as control of compliance to hand hygiene guidelines, a review of central venous catheter insertion protocols and regular search for sources of MDRAB in hospital environment, prospective follow-up of new cases was conducted. Antimicrobial sensitivity profiles were assessed for the period from 2013 until 2015. Data were processed with the statistical software WHONET 5.5. Bacteria identification and antibiotic susceptibility testing were performed by VITEK 2 compact, BioMerieux, France. The prevalence of MDRAB in the period 2009 to 2013 increased from 71 to 217 cases per year, but from between 2013 (time of implementing infection control measures) and 2015 it decreased to 113 cases in 2015. In the three year period (2013–2015), the proportion of MDRAB causing bloodstream infections (BSI) and central nervous system infections (CNSI) was 15.85% from all identified MDRAB cases. Of the 113 MDRAB infections diagnosed in 2015, BSI was found in 16.81% cases (n = 19). Antibiotic resistance testing showed that colistin is the most effective drug against MDRAB. The majority of* Acinetobacter baumannii *isolates were resistant to Ampicillin/Sulbactam, Piperacillin/Tazobactam, Ceftazidime, Cefepime, Imipenem, Meropenem, Amikacin, Gentamicin, Tobramycin, and Ciprofloxacin. Over the last two years (2014–2015), prevalence of MDRAB infections decreased considerably. In the time period from 2013 to 2014, resistance of* Acinetobacter baumannii *increased to imipenem, ciprofloxacin and colistin, while decreased slightly to amikacin. Rigorous infection control measures, such as identification and elimination of new MDRAB sources in environment, review of the central venous catheter insertion protocol and improvements in hand hygiene, are crucial for decreasing distribution of and invasive infections caused by MDRAB in the hospital environment.*

Key words: *multidrug-resistant* Acinetobacter baumannii *(MDRAB), infection control, resistance, bloodstream infections, colistin.*

INTRODUCTION

In the last decade there has been increasing prevalence of infections caused by multidrug-resistant organisms (MDRO), including by multidrug-resistant *Acinetobacter baumannii*. MDRAB is among the most difficult antimicrobial-resistant gram-negative bacilli to manage. Most common healthcare-associated infections caused by MDRAB are nosocomial pneumonia (especially ventilation pneumonia), central venous catheter infections, urinary tract infections, surgical site infections, skin and soft tissue infections and meningitis (Maragakis and Perl, 2008). Bacteraemia often develops leading to invasive infection (when bacteria are isolated from blood and/or cerebrospinal liquor) with a bad prognosis.

Bacteremia is a very common complication, especially in ICU due to catheter colonisation. Usually it develops on av-

erage 26 days after admission (Peleg *et al*., 2008). Depending on the source, *Acinetobacter baumannii* accounts for about 1.5 to 2.4% of healthcare associated bloodstream infections. In France, *Acinetobacter baumannii* accounted for 12% of bloodstream infections (Fournier and Richet, 2006). Over 90% of infections with *Acinetobacter baumannii* are recognised to be hospital-acquired, while only 4% are community-acquired, mostly pneumonia cases. In general, *Acinetobacter baumannii* accounts for a mortality rate in ICU of about 60%. There are few studies that provide exact numbers of infected persons, as it is very difficult to discern true infection from only colonization. The biggest problem is, when MDRAB is recognized, how to treat it?

In 2014, WHO released a publication on the threat of increasing antimicrobial resistance (Anonymous, 2014b). The main focus was on carbapenems, as this antimicrobial agent is mostly used as last resort for treating many infections. In 2009, European surveillance data showed that 17% of bacteremia infections in ICU and almost 12% of UTI infections in ICU were caused by *Acinetobacter spp*.

Highest data was seen in Italy, Lithuania, and Slovakia. Survey has been conducted in several countries of resistant strains of *Acinetobacter baumannii* isolates, and up to 80% of strains have proven to have carbapenem resistance and 47% imipenem resistance. US-wide surveillance data showed that prevalence of carbapenem-resistant strains has increased from 5.2% in 1999 to 40.8% in 2010.

Acinetobacter baumannii (genospecies 2 of the ACB complex — *A. calcoaceticus–A. baumannii*) is the most resistant strain of *Acinetobacter spp*. It harbours various genes, which makes it resistant to multiple antimicrobial agents, the most common being: beta-lactamase genes (genes coding for aminoglycoside-modifying enzymes), disinfectant-sulfanilamide resistance (*qacEDelta1-sul1*) genes, class 1 integrase (*intl1*) gene, the *qnr* gene associated with plasmid-mediated quinolone resistance, and OXA-type genes for carbapenem-resistance (type 51 (Europe), and 23 and 58 (USA) being the most common ones) (Anonymous, 2014b).

Septic shock develops in up to one-third of patients with bacteraemia. There is a trend of increasing MDRAB resistance to various widely used antibiotics and sometimes few options are available for saving a patient's life. Timely implementation of infection control measures, such as hand hygiene (Gould *et al*., 2010), control of central venous catheter insertion protocols (Bishop *et al*., 2007; Anonymous, 2012b) and hospital environmental MDRAB infection control (Anonymous, 2003; Obeidat *et al*., 2014) are extremely important to decrease spread of MDRO including MDRAB in the hospital environment and also decrease carriage of MDRO in out-patient setting.

MATERIALS AND METHODS

Rīga East University Hospital is one of the biggest health care institutions in Latvia, comprising 2120 beds, including 78 beds in Intensive Care Units (ICU). In 2014, the hospital provided health care services to 72 404 in-patients and 320 700 out-patients, including patients in ICU. There were 28 418 surgeries performed in 2014. A retrospective study was conducted of patients admitted to Rīga East University Hospital (REUH) from 2009 until 2012 and prospective follow-up of new cases after implementing of infection control measures since the beginning of 2013. The following infection control measures have been implemented: review of all protocols that guide insertion of invasive devices including central venous catheter, identifying sources of MDRAB in the hospital (ventilation systems, ventilators of computers), and control of hand hygiene in all departments of the hospital.

Data were collected based on clinical situations, and cultures were taken from blood, cerebrospinal fluid, bronchial specimens and swabs from wounds.

Bacteria identification and antibiotic susceptibility testing were performed using a VITEK 2 compact, BioMerieux, France.

Acinetobacter baumannii isolates were tested for sensitivity to ampicillin-sulbactam (SAM), piperacillin-tazobactam (TZP), ceftazidime (CAZ), cefepime (FEP), imipenem (IPM), meropenem (MEM), amikacin (AMK), gentamicin (GEN), tobramycin (TOB), ciprofloxacin (CIP), colistin (COL) and tigecycline (TGC).

Acinetobacter baumannii isolates were considered as multi-drug resistant (MDRAB) if bacteria showed combined resistance to ampicillin-sulbactam (SAM), piperacillin-tazobactam (TZP), antipseudomonal cephalosporins (CAZ, FEP), fluoroquinolones (CIP), aminoglycosides (AMK, GEN, TOB) and carbapenems (IPM, MEM).

Infection based on MDRAB-related infection was confirmed on the basis of case definitions of healthcare-associated infections (Anonymous, 2012a).

Data were processed with statistical software WHONET 5.5.

RESULTS

In the time period from 2009 to 2013, prevalence of MDRAB in Rīga East University Hospital Clinical Centre Gaiļezers increased from 71 to 207 cases per year, followed by a decrease to 113 cases in 2015 (Fig. 1). The maximum number of cases was observed in 2013 when 217 isolates were recorded.

Compared to the situation in other clinical centres of Rīga East University Hospital — Biķernieki (BIK), Linezers (LIN), Oncology Centre of Latvia (LOC), Latvian Centre of Infectious Diseases (LIC), and Centre of Tuberculosis and Lung Diseases (TBC), the decrease prevalence of MDRAB in the clinical centre Gaiļezers has been most prominent (Fig. 2).

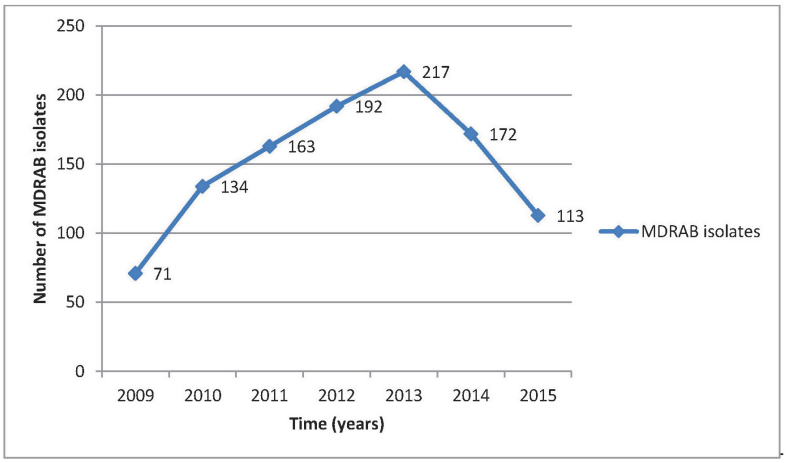

Fig. 1. Number of MDRAB isolates over years in the Rīga East University Hospital Clinical Centre Gaiļezers.

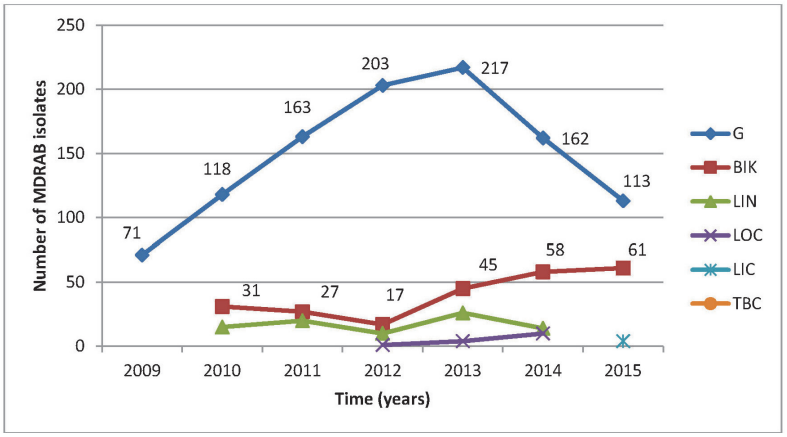

Fig. 2. Number of MDRAB isolates in clinical centres of Rīga East University Hospital. G, Gaiļezers; BIK, Biķernieki; LIN, Linezers; LOC, Oncology Centre of Latvia; LIC, Latvian Centre of Infectious Diseases; TBC, Centre of Tuberculosis and Lung Diseases.

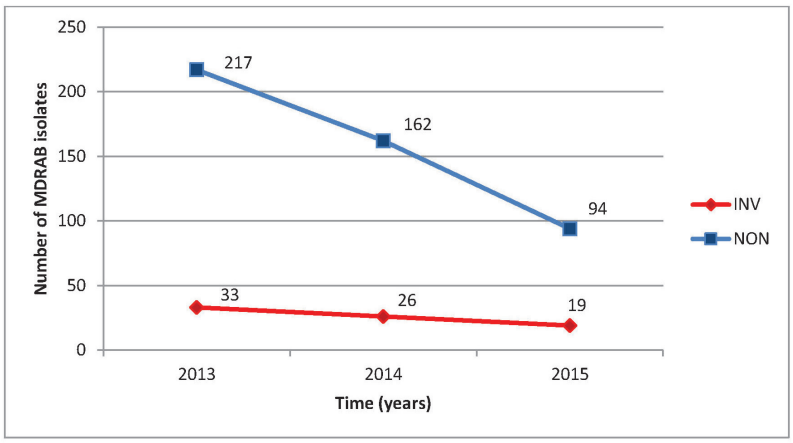

Fig. 3. Number of bloodstream infections and central nervous system infections (INV) and other site infection or colonisation (NON) MDRAB cases in the period 2013–2015.

Table 1

BLOODSTREAM AND CNS INFECTIONS IN 2013–2015

Type of infection	Number of cases	% of total invasive infections	Comment
Bloodstream infection	72	92.31%	Central venous catheter related sepsis in 46 patients (63.89%)
Meningitis	6	7.69%	No meningitis cases in 2015
Total	78	100%	

The proportion of bloodstream and CNS infections by MDRAB was 15.85% or 78 cases (Table 1).

In 2013, there were 33 MDRAB isolates from blood and cerebrospinal fluid indicating invasive infection while in 2014 this number decreased to 26 and further to 19 cases in 2015.

A decreasing tendency occurred between 2013 and 2015 in cases of MDRAB infection (Fig. 3).

All patients with bloodstream infections and central nervous system infections were treated with colistin, which was administered via intravenous and intrathecal routes for patients with meningitis.

In patients with bloodstream infections and central nervous system infections, resistance of *Acinetobacter baumannii* to various antibiotics was reported in 2013 to occur in over 80% of cases (Table 2).

Table 2

RESISTANCE OF *ACINETOBACTER BAUMANNII* TO VARIOUS ANTIBIOTICS IN 2013

Antibiotic	Abbreviation	%R (% of resistant)	%R 95%C.I.
Ampicillin/Sulbactam	SAM	87.1	69.2–95.8
Piperacillin/Tazobactam	TZP	87.9	70.9–96.1
Ceftazidime	CAZ	87.1	69.2–95.8
Cefepime	FEP	84.4	66.5–94.1
Imipenem	IPM	87.9	70.9–96.1
Meropenem	MEM	92.3	73.4–98.7
Amikacin	AMK	80	60.9–91.6
Gentamicin	GEN	77.4	58.4–89.7
Tobramycin	TOB	78.1	59.5–90.0
Ciprofloxacin	CIP	87.1	69.2–95.8
Colistin	COL	0	0.0–13.7

Table 3

RESISTANCE OF *ACINETOBACTER BAUMANNII* TO VARIOUS ANTIBIOTICS IN 2014

Antibiotic	Abbreviation	%R (% of resistant)	%R 95%C.I.
Ampicillin/Sulbactam	SAM	87.5	66.5–96.7
Piperacillin/Tazobactam	TZP	91.7	71.6–98.6
Ceftazidime	CAZ	92	72.5–98.6
Cefepime	FEP	91.7	71.6–98.6
Imipenem	IPM	92.3	73.4–98.7
Meropenem	MEM	92	72.5–98.6
Amikacin	AMK	76.9	55.9–90.2
Gentamicin	GEN	80.8	60.0–93.7
Tobramycin	TOB	76.9	55.9–90.2
Ciprofloxacin	CIP	92.3	73.4–98.7
Colistin	COL	4	0.2–22.3

In REUH, colistin is mainly used to treat infections caused by *Acinetobacter baumannii* and resistant strains reached very high numbers in 2013.

In 2014, resistance of *Acinetobacter baumannii* to various antibiotics was reported to be above 90% in most cases, which was an alarming increase compared to the level in previous years (Table 3).

Comparing data from 2013 and 2014, resistance of *Acinetobacter baumannii* increased to imipenem, ciprofloxacin and colistin, while decreased slightly to amikacin.

Imipenem resistance in 2013 was observed in 87.9% (95% CI = 70.9–96.1) isolates, while in 2014–92.3% (95% CI = 73.4–98.7), showing an increasing tendency. Also, resistance to ciprofloxacin increased from 87.1% (95% CI = 69.2–95.8) in 2013 to 92.3% (95% CI = 73.4–98.7) in 2014. Amikacin resistance decreased slightly from 80% (95% CI = 60.9–91.6) in 2013 to 76.9% (95% CI = 55.9–90.2) in 2014.

Resistance to colistin increased from 0% (95% CI = 0.0–13.7) in 2013 to 4% (95% CI = 0.2–22.3) in 2014.

DISCUSSION

Our study indicated a relatively high prevalence of MDRAB isolates in patients treated in the Rīga East University Hospital Clinical Centre Gaiļezers. The percentage of patients infected with MDRAB that had combined resistance to fluoroquinolones (CIP), aminoglycosides (GEN, TOB) and carbapenems (IPM, MEM) in REUH was 76.9–92.3%.

Data of the European Centre of Disease Prevention and Control (ECDC) on invasive *Acinetobacter spp*. number and resistance in 2013 in the EU/EEA countries (Anonymous, 2014a) suggest that Latvia could be among worst performing countries, along with Greece, Bulgaria, Croatia, Italy, Spain, and Portugal.

There has been an endemic spread of MDRAB in the Rīga East University Hospital.

This is both a clinical and public health problem that needs to be addressed with full seriousness. Spread of MDRAB not only substantially limits antimicrobial treatment options, but also creates difficulties for effective infection control in the hospital. Successful infection control measures, identification and elimination of new MDRAB sources in environment, review of the central venous catheter insertion protocol and improvements in hand hygiene are crucial for decreasing frequency of MDRAB spread in hospital environment and serious invasive infections caused MDRAB.

The high resistance level will complicate the situation in the future because of the need to use reserve antibiotics. The appearance of *Acinetobacter baumannii* resistance to colistin in 2014 is particularly alarming.

Apparently, contact isolation of patients is not sufficient to stop spread of MDRAB in the hospital setting and airborne infection isolation is necessary.

Among bloodstream infections, a large numbers of patients received central venous catheter-related sepsis (63.89%). This indicates a need to further review the central venous catheter insertion procedure.

In order to reduce unnecessary use of antibiotics, it is very important to clearly distinguish colonisation from invasive infections.

It is very important to delay selection of pan-resistant *Acinetobacter baumannii* and other resistant gram-negative flora by controlling and mastering correct antibiotic use in REUH as well as antibiotic stewardship and improving surveillance networks.

CONCLUSIONS

Over the last two years (2014–2015), prevalence of MDRAB infections has decreased considerably. Resistance

of *Acinetobacter baumannii* is of concern in REUH. Resistance increased to imipenem, ciprofloxacin and colistin, while decreased slightly to amikacin from 2013 to 2014. Systematic implementation of infection control measures like identification and elimination of new MDRAB sources in the environment, review of the central venous catheter insertion protocol and improvements in hand hygiene are crucial for decreasing frequency of MDRAB spread in the hospital environment and invasive infections caused by MDRAB.

REFERENCES

Anonymous (2003). Centers for Disease Control and Prevention (CDC). Guidelines for environmental infection control in health-care facilities: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *Morb. Mort Weekly Rep*., **52** (No. RR-10), 1–48.

Anonymous (2012a). *Point prevalence survey of healthcare associated infections and antimicrobial use in European acute care hospitals — protocol version 4.3.* ECDC technical document. European Centre for Disease Prevention and Control. ECDC, Stockholm, pp. 43–63.

Anonymous (2012b). Practice Guidelines for Central Venous Access. A Report by the American Society of Anesthesiologists Task Force on Central Venous Access. The American Society of Anesthesiologists. *Anesthesiology*, **116**, 539–573.

Anonymous (2014a). *Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).* European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2013. ECDC, Stockholm.

Anonymous (2014b). *Antimicrobial Resistance: Global Report on Surveillance.* WHO, pp. 69–71.

Gould, D. J., Moralejo, D., Drey, N., Chudleigh, J. H. (2010). Interventions to improve hand hygiene compliance in patient care. *Cochrane Database Syst. Rev*., Issue 9. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005186.pub3/epdf

Bishop, L., Dougherty, L., Bodenham, A., Mansi, J., Crowe, P., Kibbler, C., Shannon, M., Treleaven, J. (2007). Guidelines on the insertion and management of central venous access devices in adults. *Int. J. Lab. Hem.,* **29**, 261–278.

Maragakis, L. L., Perl, T. M. (2008). Acinetobacter baumannii: epidemiology, antimicrobial resistance, and treatment options. *Clin. Infect. Dis*., **46** (8), 1254–1263.

Obeidat, N., Jawdat, F., Al-Bakri, A. G., Shehabi, A. A. (2014). Major biologic characteristics of *Acinetobacter baumannii* isolates from hospital environmental and patients' respiratory tract sources. *Amer. J. Inf. Control*, **42,** 401–404.

Peleg, A. Y., Seifert, H., Paterson, D. L. (2008). *Acinetobacter baumannii*: emergence of a successful pathogen. *Clin. Microbiol. Rev.,* **21** (3), 538–582.

Fournier, P. E., Richet, H. (2006). The epidemiology and control of *Acinetobacter baumannii* in health care facilities. *Clin. Infect. Dis*., **42** (5), 692–699.

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MULTIREZISTENTĀS *ACINETOBACTER BAUMANNII* IZPLATĪBAS MAZINĀŠANĀS RĪGAS AUSTRUMU KLĪNISKAJĀ UNIVERSITĀTES SLIMNĪCĀ

Rīgas Austrumu klīniskajā universitātes slimnīcā (RAKUS), kas ir lielākā stacionārās aprūpes iestāde Latvijā, pēdējo gadu laikā ir izteikta tendence pieaugt inficētībai ar multirezistento *Acinetobacter baumannii* (MRAB) slimnīcā. *Acinetobacter baumannii* ir gram-negatīvs, strikti aerobs, neizvēlīgs, nefermentatīvs patogēns, kurš kā patogēns tiek identificēts ar veselības aprūpi saistītu infekciju gadījumos: ar veselības aprūpi saistīta pneimonija (īpaši ar mākslīgo plaušu ventilāciju saistīta pneimonija), centrālo asinsvadu katetru infekcijas, urīnceļu infekcijas, ķirurģiskās brūces infekcijas un cita veida brūces infekcijas. MRAB sagādā īpašas raizes praksē, jo tā izraisīto infekciju ārstēšanai praktiski ir tikai viens antibakteriāls līdzeklis — kolistīns. MRAB izplatības apmēra apzināšanai tika apkopoti 2009.–2015. gadu dati, bet jutības profilam — 2013.–2014. gadu dati. 2013. gadā tika pārskatīti centrālo venozo katetru ievietošanas protokoli, veiktas roku higiēnas intervences un meklēti MRAB avoti slimnīcas vidē. MRAB izplatība RAKUS pieaug kopš 2009. gada, kad tika konstatēts 71 gadījums, 2013. gadā — 217 gadījumi, bet 2014. gadā — 172 gadījumi un 2015. gadā vairs tikai 113 gadījumi. No asinīm un lumbālpunktāta izdalīto MRAB skaits: 2013. gadā — 33 gadījumi, 2014. gadā — 26 gadījumi, 2015. gadā — 19. Imipenēma rezistence 2013. gadā — 87.9 % (95 % CI = 70.9–96.1), 2014. gadā — 92.3 5 (95 % CI = 73.4–98.7); amikacīna rezistence 2013. gadā — 80 % (95% CI = 60.9–91.6), 2014. gadā — 76.9 % (95% CI = 55.9–90.2), bet kolistīna rezistence 2013. gadā — 0% (95 % CI = 0.0–13.7), 2014. gadā — 4% (95 % CI = 0.2–22.3). Salīdzinot RAKUS datus un Eiropas slimības profilakses centra uzraudzības datus par antimikrobiālās rezistences uzraudzību Eiropas Savienībā/Eiropas Ekonomiskajā Savienībā, secināms, ka RAKUS ir endēmiska invazīvo MRAB izplatība. Konstatēts zems MRAB saistītu asinsstraumes un CNS infekciju īpatsvars (15.16%). Asinsstraumes infekciju vidū augsts ar centrālo venozo katetru saistītu sepses gadījumu (62.26% no asinsstraumes infekcijām). MRAB pacientu izolācijā nav pietiekoša kontakta tipa izolācija. Kopš 2013. gada vērojama MRAB skaita mazināšanās, kas ir saistīta ar sekmīgu centrālo venozo katetru ievietošanas protokolu ieviešanu, veiktajām roku higiēnas intervencēm un jaunu MRAB avotu identifikāciju un to novēršanu slimnīcas vidē.