Ph.D. Thesis

Hospital hygienic surveillance studies and their application

Márta Patyi, M.D.

Supervisor:

Edit Hajdú M.D., Ph.D., Department of Infectology, University of Szeged

Szeged

2015

LIST OF FULL PAPERS THAT SERVED AS THE BASIS OF THE PH.D. THESIS

I. **Patyi M**
A széles spektrumú béta-laktamáz termelő kórokozók, mint egy újabb kórházhigiénés problémakör intézményünkben
Infekció & Infekciókontroll 2009;**1**:59-66.

II. **Patyi M**, Varga É, Kristóf K
Curiosities of the methicillin-resistant Staphylococcus aureus survey- possibility of pseudo-outbreak and transmission to household contacts
Acta Microbiol Hung 2011;**2**:135-144.
IF:**0.787**

III. **Patyi M**, Sejben I, Cserni G, Sántha B, Gaál Z, Pongrácz J, Oberna F
Retrospective Health-care Associated Infection Surveillance in Oral and Maxillofacial Reconstructive Microsurgery
Acta Microbiol Hung 2014;**4**:407-416.
IF:**0.780**

IV. **Patyi M**, Varga É, Tóth Zs
Neonatalis Intenzív centrumunkban jelentkező széles spektrumú béta-laktamáz termelő kórokozók halmozódása miatt hozott intézkedéseink, azok eredménye és fenntartása
IME - Az egészségügyi vezetők szaklapja
2015;**2**:9-11.

V. **Patyi M**, Varga É, Svébis M
Probléma baktériumok előfordulása intézményünkben (Occurance of problem bacteria in our hospital)
Egészségtudomány
Accepted: 30.01.2015, Anticipated date of publication: September 2015

LIST OF ABSTRACTS THAT SERVED AS THE BASIS OF THE PH.D. THESIS

VI. **Patyi M,** Tóth Zs
Széles spektrumú béta-laktamázt termelő Gram negatív kórokozók előfordulása Intézményünk PIC-Koraszülött Részlegén
Magyar Infekciókontroll Egyesület XIII. Kongresszusa
Székesfehérvár, 04-06.06.2009
Book of abstracts p. 41.

VII. **Patyi M,** Varga É
Clostridium difficile terjedésének megakadályozására szolgáló protokollunk
Magyar Infekciókontroll Egyesület XIV. Kongresszusa
Balatonvilágos, 27-29.05.2010
Book of abstracts p. 34.

VIII. **Patyi M,** Varga É
Multirezisztens kórokozókra vonatkozó adataink összesítése 1996-2009.között
XVI. Kórházhigiénés Ankét
Galyatető, 17-18.09.2010
Book of abstracts p. 32.

IX. **Patyi M**, Herczeg É
Multirezsiztens Pseudomonas – Gondolkodjunk együtt!
Magyar Infekciókontroll Társaság XV. Kongresszusa
Pécs, 26-28.05.2011
Book of abstracts p. 37.

X. **Patyi M**, Székeli S, Varga É, Gera L
Multirezisztens kórokozók által okozott nosocomialis infekciók a Traumatológiai osztály 4 éves anyagában
A Magyar Traumatológus Társaság 2012. évi Kongresszusa
Eger, 07-09.06.2012
Book of abstracts p. 71.

XI. **Patyi M**, Sántha B, Sejben I, Cserni G, Gaál Z, Oberna F
Szájüregi, szájgarati mikrosebészeti műtétek esetén felmerülő nosocomialis infectiok és az alkalmazott antibiotikus profilaxis retrospektív vizsgálata
Magyar Arc-, Állcsont- és Szájsebészeti Társaság 16. Nemzeti Kongresszus
Visegrád, 22-24.11.2012
Book of abstracts p. 64.

XII. **Patyi M,** Herczeg É
Multirezisztens kórokozókkal kapcsolatos betegtájékoztatók intézményünkben
Kórházhigiénés Ankét
Herceghalom, 02-04.10.2014
Book of abstracts p. 40.

1. INTRODUCTION

1.1 Surveillance

Continuous prospective surveillance in hospital settings usually means the active collection of data concerning healthcare-associated infections (HCAI) connected with hospital care. These data refer to the incidence and epidemiology of a certain disease, the regular analysis of which enables us to take the necessary preventive measures to avoid spreading of pathogens. Surveillance activity is practised in two basic forms: in a retrospective and in a prospective way. It can be a continuous programme or a point prevalence survey of a short period. All of the patients in a hospital or in a unit can be involved, or it can be also limited to a certain disease. Before the actual surveillance activity, a plan is to be worked out which has the following general steps:

- Choice of surveillance methodology
- Selection of the population to be investigated
- Definition of the outcome
- Choice of time period
- Studying surveillance definitions
- Choice of data to be collected
- Selection of methods for data analysis
- Defining stakeholders to receive surveillance report
- Writing a surveillance plan

In this thesis, I deal with 2 types of surveillance. The first one is a continuous, active, prospective surveillance based on microbiological results regarding problem bacteria. The second one is a retrospective surveillance based on medical records regarding oral and oropharyngeal microsurgery.

Problem bacteria as causes of HCAIs present an ever increasing burden. Microbes which belong to this group of pathogens are difficult to detect or identify, and the diseases caused by them pose a therapeutic challenge.

The discovery of penicillin in 1928 was followed by the discovery and commercial production of many other antibiotics. The widespread use, inappropriate and overuse of antibiotics lead to emerging drug resistance in bacteria: some strains of pathogens became resistant to one certain drug, but more strains developed resistance to many antibiotics, the phenomenon of multidrug resistance.

Gram-positive multidrug-resistant bacteria (MDRB) are usually present in the nose, throat, on the skin, whereas Gram-negative bacteria are found in the colon as a colonizing

flora. The exceptions to this general rule will be discussed later. A colonized person has no symptoms of infection, but the samples taken from one or more parts of his/her body sites (e.g. nose, throat, axilla, perineum, stool) show aberrant flora containing a pathogen. Colonization can be transient, intermittent or chronic.

The source of infection can be a colonized or an infected patient, and the symptom-free healthcare workers colonized with MDRB as well. MDRB may be transmitted by direct (from the hands of healthcare workers to the patient) or indirect (contaminated instruments or tools) contact, by airborne (important only at burn units, in case of skin diseases and in case of patients with cough and sputum production) or by vehicle transmission (e.g. infusions, drugs). MDRB infection means a symptomatic disease (e.g. wound infection, skin or soft tissue infection, pneumonia, bloodstream infection, urinary tract infection) caused by these pathogens, which can be detected by laboratory tests. HCAIs caused by MDRB are often life-threatening conditions such as pneumonia or sepsis. If the human normal flora is damaged, these resistant microorganisms can colonize not only sick people but also their family members and healthcare workers too. They are able to multiply there, spread to the environment, and be a source of infection.

Risk factors for the occurence of these problem bacteria are among others long hospital stay, treatment at intensive care unit (ICU), broad-sprectum antibiotic therapy, prematurity, old age, compromised immune system, loss of continuity of skin, malnutrition, indwelling urinary tract catheter, steroid therapy, chemotherapy and re-hospitalisation. The treatment of these infections may become problematic in the near future.

Antimicrobial resistance to antibiotics can be developed by four general ways: a. bacteria produce enzymes which inactivate or alter the drug molecules, e.g. β-lactamase of *Staphylococcus aureus*, b. change in the stucture of the target site molecule, e.g. penicillin-binding protein of *Streptococcus pneumoniae*, c. modification of external microbial surface, e.g. blocking of porin channels of *Pseudomonas aeruginosa*, d. efflux mechanisms to remove the antibiotic molecules from the microorganism, e.g. resistance to tetracyclines.

The contemporary method for complex and large tissue replacement in the oral cavity and oropharynx is microsurgical free tissue transplantation. The most frequent indication for this procedure is reconstruction following primary surgical oncological interventions. However, this method is also used in patients with traumatic lesions, developmental defects, tumour removal after primary radiotherapy, some benign diseases and osteonecrosis. Improving surgical techniques, more accurate indications for surgery and two-team operations have made the results of microsurgery more successful and have shortened the duration of

surgery. These changes have established good conditions for oncological recovery and functional rehabilitation. The success rate of microsurgical operations, delayless oncological adjuvant therapy and the acceptable quality of life of the patient are important factors that are strongly influenced by wound healing. Perioperative antibiotic prophylaxis (PAP), which is effective against the normal oral bacterial flora, is mandatory and plays an important role in polymorbid or anaemic patients who receive preoperative radiotherapy or undergo long lasting surgery involving potentially infectious sites. The strategy of PAP in reconstructive microsurgery of the head and neck remains to be clarified in some details.

While examining the practice of PAP in oral and maxillofacial surgery, I performed a retrospective surveillance based on case records of our patient material.

2. AIMS

2.1 Surveillance for multidrug-resistant bacteria

- to observe the number of cases of a certain type of MDRB in our institution from the first occurrence
- to make a distinction between imported and nosocomial cases
- to observe the number of cases of colonized and infected patients
- to define the characteristic samples of a certain MDRB
- to estimate the expected number of cases
- to estimate the expected costs and isolation demands
- to prepare the necessary modification of the guideline and the patient information leaflet on an emerging pathogen

2.2 Surveillance at the Department of Oral and Maxillofacial Surgery

- to survey the practice of PAP and the incidence of HCAIs in the special microsurgery-treated patient group of the Department of Oral and Maxillofacial Surgery
- to compare our PAP practice and HCAI rate with those in the literature
- to compare the primary and the salvage group of patients regarding HCAIs
- to give feed-back on clinical practice from the data of the retrospective surveillance
- to make a suggestion for the improvement of PAP practice of the Department of Oral and Maxillofacial Surgery, if applicable

3. MATERIALS AND METHODS

3.1 Multidrug-resistant bacteria surveillance

Based on the available hospital hygienic data from microbiological results-based surveillance, the hospital hygienic team of the Bács-Kiskun Teaching County Hospital has collected data on the following problem bacteria: methicillin-resistant *Staphylococcus aureus* (MRSA) since 1996, extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* since 2005, multiresistant *Pseudomonas aeruginosa* (MPAE) since 2006, *Clostridium difficile* (CD) since 2008, multiresistant *Acinetobacter baumannii* (MRAB) since 2010, carbapenem-resistant *Enterobacteriaceae* (CRE) since 2012, vancomycin-resistant *Enterococcus* (VRE) since 2013. The specified dates mean the first occurence of a certain type of pathogen too.

The MDRB cases from 1 January 1996 to 31 December 2014 were surveyed on the basis of the medical charts and microbiological data of the patients and health care workers. Persons were considered to be infected when they had a positive culture and had signs or symptoms of infection caused by MDRB. Persons were considered to be colonized with MDRB when they had a positive culture without any signs or symptoms of infection. A new nosocomial case was defined as occurring in a patient whose MDRB isolate was cultured more than 48-72 hours after admission. Prior culture results for MDRB registered on admission were considered as a known/imported case.

Since in terms of hospital hygienic work and costs, not the number of patients affected by problem bacteria, but the number of cases is relevant, I worked with the latter in my thesis and performed descriptive analysis of the received data.

3.2 Surveillance at the Department of Oral and Maxillofacial Surgery

Between 01 September 2007 and 31 January 2011, 108 patients underwent reconstructive microsurgical procedure at the Department of Oral and Maxillofacial Surgery and Otorhinolaryngology of the Bács-Kiskun County Teaching Hospital, Kecskemét.

The following data were processed during this retrospective analysis: type and duration of perioperative antibiotic prophylaxis (PAP), results of microbiological cultures, if any, rate of HCAI and the necessity of a tracheostomy or a percutaneous endoscopic gastrostomy (PEG). In 6 cases, the length of PAP could not be established because of inaccurate medical records, but the other relevant data were available, so these cases were included in the analysis as well. The surgical wounds were classified into one of the four groups based on the degree of contamination present at the time of surgery according to the recommendations in the medical literature.

The comparison of primary and salvage operations was made with the two-sample t-test or the Fisher exact probability test and the significance level was set at $p<0.05$.

4. RESULTS

Based on the available hospital hygienic data from microbiological results-based surveillance, 3444 cases fell into the group of problem bacteria from 1 January 1996 to 31 December 2014. In order of frequency, 42.1%, 33.2%, 21.0% and 2.8% were the proportion of ESBL-producing *Enterobacteriaceae*, MRSA, CD, MPAE, respectively; while 0.9% was the occurence of MRAB, CRE and VRE together.

The total number of MDRB cases amounted to 33 in 1996, but reached 558 in 2014. This represents nearly a 17-fold increase.

I assessed the total number of microbiological samples between 2012 and 2014 similarly to the European Centre for Disease Prevention and Control (ECDC) data collection. The number of samples has been on the increase since 2012. The number of haemocultures per 1000 hospital days ranged from 8.8 to 10.0.

I had the opportunity to collect the data of the most frequent antibiotics used to treat problem bacteria between 2012 and 2014. The days of treatment (DOT) data are given. Increased use of tigecyclin, colistin, imipenem and metronidazole was proven. It should be noted, however, that these agents are used not only to treat these infections, but also against other infective diseases, for example metronidazole is administered for PAP or to treat abdominal infections beside Clostridium difficile infection (CDI) treatment. After a registered decrease in 2013, vancomycin use increased in 2014.

4.1 Methicillin-resistant *Staphylococcus aureus*

The total number of cases was 1145. The number of inpatient cases was 684. These data were analysed according to the source of infection or colonization (new or imported), and outpatients were viewed separately from inpatients.

Since of my institution is a county teaching hospital and a lot of patients come from different types of healthcare facilities, patients are quite frequently MRSA-positive on admission or they have positive cultures within 48-72 hours. These cases are considered to be imported. 2005 was the first year when the number of cases was above 80. In that year, the largest number of new cases was detected, 60 of 86 cases. The number of cases grew steadily from 2002 to 2013. The number of known cases was the highest in 2013, 33 of 116 cases, which amounted to 28.4%. In 2014, we experienced a 17% decrease compared to the previous year. In the same year, the outpatients' number was the highest, 27 cases, which meant

28.1%. The 30 new cases in 2014 meant a 43% decrease compared to the previous year. On the basis of the data, it can be established that the number of new and known cases diminished, while the number of imported and outpatient cases rose. In 2014, we registered the highest number of imported cases (31 cases), which amounted to 32.2% of this year's cases.

I have found data among the hospital hygienic records about the MRSA-positive samples taken between 2005 and 2014. During these ten years, the positive results amounted to 1874. More than one positive sample can be taken from a patient, so the number of samples is higher than that of cases. These data are presented according to medical specialties.

Among inpatients, the most common infections by MRSA were wound infection (22.4%), skin and soft tissue infection (1%), sepsis (13.5%) and respiratory tract infection (3.1%). 373 colonization cases were observed, which amounted to 54.5%.

The incidence of new cases calculated per 1000 nursing days was the most favourable between 1998 and 2002.

In the period examined, four outbreaks and one pseudo-outbreak occurred. In the four outbreaks, only one patient died in 2009. In 1997, 10 cases of wound infection, 2 cases of colonization were detected among 12 affected patients, and one hospital worker turned out to be a carrier. In 2003, among 9 patients, one had sepsis, 2 had wound infections and six of them were colonized. Two hospital workers were nasal carriers then. In 2004, one sepsis and two wound infections were diagnosed. In 2009, two septic, and 4 colonized cases were discovered. In the last two outbreaks, no colonization or infection caused by MRSA was identified among hospital workers.

4.2 Extended-spectrum β-lactamase-producing *Enterobacteriaceae*

During the ten-year period examined, 1452 cases were detected. After the emergence of the first cases in 2005, a slow increase was observed between 2008 and 2011. In 2012, a sharp rise was noticed, despite the fact that no outbreak occurred. The number of imported cases has been significant since 2011. The number of patients with already known colonization increased in 2012. In 2014, the number of cases decreased by 37.7%, which can mainly be ascribed to measures taken in perinatal intensive care unit (PIC), by which the number of cases there went down substantially.

Between 2005 and 2014, the number of registered ESBL-positive samples was 1985.

These data are presented according to medical specialties, similarly to MRSA.

794 colonized cases, out of 976 new cases, were identified among inpatients, which amounted to 81.4%. Abdominal cavity infection occurred in 76 cases, that is 7.8%. The

diseases caused by the pathogen were as follows: 4 cases of cholangitis, 1 case of endometritis, 1 case of necrotising enterocolitis, 1 case of peritonitis, 68 cases of urinary tract infection (7%) and 1 case of vaginitis. The pathogen caused sepsis in 47 patients, which amounted to 4.8%. Other illnesses developed in 59 cases, for example decubitus infection, pneumonia and wound infection. The pathogens cultured were the following in alphabetic order: *Citrobacter amalonaticus, Citrobacter freundii, Enterobacter cloacae, Esherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus mirabilis and Serratia marcescens.*

During 10 years, 207 cases of ESBL-producing pathogen were observed in PIC. 3 cases of infection and 204 cases (98.5%) of colonization were detected.

Stool samples and anorectal swabs taken on the day of their premature birth from 335 mothers were screened for ESBL in the Obstetric Unit of our hospital. Among them 10 cases of asymptomatic ESBL-producing strain were identified in the colon. This means a colonization rate of 2.98%. From October 2013, none of the 10 ESBL-colonized mothers' premature infants were positive, and none of them became positive during the hospital stay.

4.4 Multiresistant *Pseudomonas aeruginosa*

The first MPAE strain was isolated in our hospital in 2006. During this period, 97 cases occurred. In 2009, the highest number of new cases was detected, that is 22. In 2013 and 2014, two imported cases appeared each year as well. Among outpatients, a maximum of 1 or 2 cases were found.

From 2009 to 2011, MPAE strains were deep-frozen. 19 of these deep-frozen samples (10 from 2009, 9 from 2011) were recultured and phage-typed in the National Center for Epidemiology (NCE), where no common phage type was found among the samples.

No MPAE outbreak took place during these 8 years.

The pathogen was most frequently isolated from urine, wound discharge, haemoculture and bronchial fluid.

126 MPAE positive samples were observed among inpatients between 2006 and 2014.

The microbe caused the following diseases in inpatients: 4 cases of wound infection, 3 cases of urinary tract infection, 7 cases of sepsis, 2 cases of lower repiratory tract infection and 1 case of cholangitis. It appeared as colonized flora in 80 cases, that is 82.5%.

4.5 Multiresistant *Acinetobacter*

This pathogen has been present in our institution for 5 years. During this period, MRAB was cultured in 33 samples from 15 patients. It did not occure in outpatients.

In the period studied, the pathogen gave rise to 8 cases of infection and 7 cases of colonization. The distribution of infections is as follows: 1 case in 2010, 2 cases in 2012, 3

cases in 2013 and 2 cases in 2014. The distribution of diseases according to organ involvement is as follows: 6 cases of sepsis, 1 case of lower respiratory tract infection and 1 case of upper respiratory tract infection. The number of colonized cases was 1-1 in 2010 and 2011 respectively, while 4 in 2014. The microorganism was cultured from the following sites: skin, bronchus discharge, drain, haemoculture, abdominal fluid, cannula, sputum, nose, wound discharge, throat, trachea and urine.

4.6 Carbapenem-resistant and carbapenemase-producing *Enterobacteriaceae*

CRE emerged in our hospital 3 years ago. It was cultured from 10 samples of 6 patients. 2 cases were identified in 2012, and 4 in 2014. 5 patients were in PIC and 1 in internal medicine unit. The pathogen was *Klebsiella pneumoniae* in every case. It was cultured from 2 samples in 2012, and from 8 in the following year. 1 nose, 1 trachea, 2 haemoculture and 6 stool samples were positive. It gave rise to one sepsis case in 2012. It appeared as colonizing flora in the other cases.

We haven't detected carbapenemase-producing *Enterobacteriaceae* (CPE) in our hospital yet.

4.7 Vancomycin-resistant *Enterococcus*

The pathogen emerged in our hospital in 2013, as a consequence of the transfer of a patient with a wound infected by VRE from a university institution. It was cultured from 10 samples of 5 patients. The distribution of these was: 2 haemocultures, 2 wound discharges, 2 abdominal fluids and 4 stool samples. It has occurred in two units, in intensive care unit (ICU) and Invasive Cardiology Unit. It led to 2 cases of sepsis, 1 case of wound infection and 2 cases of colonization.

4.8 *Clostridum difficile*

From 2008 to 2014, 724 cases of CDI occurred. The total number of cases was found to increase sharply from 2011. The increase slowed down from 2012. The first 5 imported cases were observed in 2010, and 38 cases were registered 4 years later. 456 cases (63%) occurred in internal medicine units, where the antibiotic use is higher than in surgical units.

It is difficult to follow up the recurrences, if the patient is not readmitted to hospital. 3 definitive recurrent cases were found in 2011, while 19 cases in 2014. The real number must be much higher.

In the period studied, 3 outbreaks were identified. The first epidemic affecting 18 people took place in an internal medicine unit from 29 February to 14 April 2012. In the second outbreak, 5 patients were affected in an other internal medicine unit between 28 December 2012 and 6 February 2013. From 3 January to 16 March 2014, the third outbreak

occurred in the internal medical unit, where the first epidemic has occurred 2 years before. 24 patients were registered then. The presence of 027 phage type was proven by phage typing in all 3 outbreaks.

4.9 Surveillance at the Department of Oral and Maxillofacial Surgery

According to the wound classification, 107 surgical procedures belonged to category B and one to category D. The indications for the operations were malignant tumors in 99 cases (88 oral and 11 extraoral tumours), and benign diseases in 9. There were 80 male (75%) and 28 female (26%) patients in this study. Their mean age was 56.4 years (range: from 23 to 84 years). The average operation time was 322 minutes (range: from 180 to 1070 minutes). The average duration of hospital stay was 17.3 days. Primary and salvage operations were carried out in 70 cases (65%) and in 38 cases (35%), respectively. In 89 cases, soft tissue flaps, and in 19 cases bone flaps were used.

Two patients (2%) were administered chemotherapy before surgery and two (2%) received prior radiotherapy, fourteen patients (13%) underwent previous surgery and radiotherapy, four patients (4%) received prior surgery with radio- and chemotherapy, nine patients (8%) underwent previous surgery and seven patients (6%) received previous radio- and chemotherapy.

HCAIs were diagnosed in 10 cases (9.3%), including 8 surgical site infections (SSIs) and 2 instances of pneumonia. The pathogens cultured from SSI cases were the following: *Pseudomonas aeruginosa*, *Serratia* sp., *Klebsiella* sp., *Proteus mirabilis*, *Enterobacter* sp. and coagulase-negative *Staphylococcus*. In one case, the wound infection was caused by MRSA.

Except from one case, more than one pathogenic agent was identified in the infected wounds. All HCAI cases occurred in patients who had undergone category B operations. 7 cases (6.5%) consisting of 5 SSIs and the 2 cases of pneumonia were recorded with primary procedures. Three cases (2.8%) of SSI occurred in patients undergoing salvage operations. The HCAI rate of primary and salvage surgical procedures were 7/70 (10%) and 3/38 (7.9%), respectively. There was no statistical difference between these two rates (p=1, Fisher exact test). Seventeen patients (16%) needed tracheostomy and two received PEG. With patients having tracheostomy, the average length of antibiotic use was 12.7±10.4 days. Three cases (2.8%) of wound infection and one case of pneumonia occurred in this group. So the HCAI rate among them was remarkably high (23.5%), and higher than the rate seen in patients not in need for tracheostomy or PEG (p=0.049, Fisher exact test). There was no significant difference in the proportion of HCAI cases found after operations using soft tissue flaps (10.1%) or bone flaps (5.3%) (p=0.69, Fisher exact test).

Total and partial flap losses occurred in 2-2 cases (2-2%), respectively. One patient died. He was reoperated on for a cervical haematoma compressing the flap on the 9th postoperative day. Two days later, after extubation, obstructive respiratory failure developed. Conicotomy and tracheostomy were performed, but his life could not be saved. No autopsy was done.

The average length of antibiotic prophylaxis in the 102 patients with available data was 8.3±5.2 days (range: from a single dose to 39 days) .The average length of PAP was 8.0±4.3 days for primary operations and 8.9±6.7 days for salvage operations. The two-sample t-test showed no significant difference between the duration of PAP in these two subgroups (p=0.41). The antibiotic prophylaxis was continued in 3 cases, when wound infection or pneumonia was diagnosed. In 7 cases, the antibiotic was changed to another one. Counting only the cases in which no HCAI occurred (98 cases, 90.1%) the duration of antibiotic administration could be determined (94 cases, 87%): the average duration of antibiotic regimens was 7.6 days.

5. DISCUSSION

5.1 Multidrug-resistant bacteria

Until the end of the studied period (31 December 2014), the NCE published national guidelines only on MRSA and CD. So until that time, local hospital hygienic protocols determined the necessary MDRB sreening tests in Hungarian hospitals. Therefore, data of the institutions were not comparable with each other, since the number of cases was higher in hospitals which performed screening test, but much lower in institutions where no screening tests were done.

The screening tests are regulated and performed according to the MDRB protocol of our hospital.

It is obvious that the costs of isolation, microbiological tests and treatment of MDRB patients put significant burden on the hospital.

Nosocomial infections are the main cause of extra costs in healthcare and are a question of patient safety. About 30% of HCAIs can be prevented effectively with infection control and adequate screening methods.

According to the report of European Centre for Disease Prevention and Control (ECDC) in 2011, in which the number of haemocultures per 1000 patient days was given, this value was 7.5, 14.1, 46.7 and 91.3 in Bulgaria, Austria, Ireland and Italy, respectively. This value has increased slowly in our hospital, but it is quite low, ranges between 8.8 and 10.0.

Data regarding problem bacteria in the United States of America (USA) were published by the Centers for Disease Control and Prevention (CDC) in 2013.

The Healthcare-associated Infections Progress Report in 2015 stated that the number of HCAIs was lower than 2 years before. The number of central line-associated bloodstream infections decreased by 46% between 2008 and 2013, while the reduction of surgical site infections (SSI) was 19% in the same period. However, the number of catheter-associated urinary tract infections increased by 6% from 2009 to 2013. These data underline the importance of appropriate antibiotic policy and adherence to hospital hygienic rules.

According to the data of CDC in 2013, the pathogens discussed cause at least 2 049 442 infections and 23 000 deaths yearly in the USA.

Data published by the NCE in 2013 showed that the number of reported infections caused by MDRB had increased in our country over the period 2005-2012. While 733 cases were registered in 2005, this number was 3263 in 2012. Number of deaths caused by MDRB infection rose from 161 in 2005 to 876 in 2012. One of the causes of this increase may be that at the beginning of the reporting system in 2005 only 53 institutions reported their data, whereas 84 institutions participated in reporting in 2012. The HCAIs' rate per 10 000 discharged patients was 11.4 in 2011. Our hospital has fulfilled this obligation from the beginning.

Based on the available hospital hygienic data from microbiological results-based surveillance, the ever-growing number of MDRB and CDI cases is well indicated by the increasing consumption of antibiotics used to treat these infections.

5.2 Methicillin-resistant *Staphylococcus aureus*

Nowadays, MRSA is one of the main nosocomial pathogens. According to the data of the CDC, it causes 80 461 severe infections and 11 285 deaths per year in the USA. Between 2011 and 2013, the number of MRSA bacteriaemia was reduced by 8%.

We established a protocol, which contains the tasks to be performed when an MRSA positive case occurs in the hospital. The protocol is based on the current national guidelines. The infection control measures in Europe vary from country to country, but they are uniform regarding isolation, screening and protective equipment.

Our outbreaks and pseudo-outbreak underline the necessity of phage-typing the pathogen, because on the basis of the antibacterial sensitivity pattern, the claimed cases could not been classified exactly as outbreaks or sporadic cases. The occurrence of the seven different phage-types of MRSA in the Nursing Unit suggests that the risk of MRSA infection or colonization is higher in this type of unit.The following infection control measures were

introduced in our hospital: prompt education on hand hygiene and isolation rules in Nursing Unit, hand hygiene compliance testing in every unit of the hospital, revision of MRSA protocol, extension of routine screening and the annual hospital hygiene education includes hand hygiene and isolation rules apart from local problems and tasks.

We suggested to the management that the cost of routine screening should be covered by the central budget of the hospital, so it does not increase the expenses of the given unit, which would encourage more frequent sampling.

We were able to reduce the number of cases in 2014.

5.3 Extended-spectrum β-lactamase-producing *Enterobacteriaceae*

Each year in the USA, 26 000 infections and 1700 deaths are attributed to this pathogen. The treatment costs of a single infection amount to 40 000 $.

The colonization rate of ESBL-producing bacteria is significantly higher than that of MRSA. The most frequent disease caused by this pathogen is abdominal infection. The necessary hospital hygienic rules are the same as for MRSA. The 2.98% positivity of the screening tests done among asymptomatic pregnant women on the day of their premature birth may indicate a fairly high incidence in the general population. The large drop in the number of cases in our PIC unit was achieved by reevaluation of antibiotic policy, acquisition of new equipment, regular hygienic education and better hand hygiene compliance. The lack of appropriate decolonisation strategy and unequivocal patient clearance methods present immense problems.

2014 was the first year when the continuous growth of the number of cases ceased and we registered a decrease.

5.4 Multiresistant *Pseudomonas aeruginosa*

This microbe gives rise to 6700 infections and kills 440 people yearly in the USA.

The MPAE is one cause of the reintroduction of colistin (also known as polymyxin E) into the therapy in Hungary. The multiresistant Gram-negative bacilli (eg. *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*) are still sensitive to this chemical. There is a study on the application of specific bacteriophages against the proper bacteria. But first of all, the most important would still be to keep the hygienic rules (disinfection, isolation) and the proper application of antibiotics.

Because of the clustering of same resistance profile pathogens in the ICU, the possibility of an outbreak emerged, which was contradicted by the results of the phage typing. The cases proved to be sporadic ones. Since the situation could not be clarified otherwise, the role of phage typing is essential too.

This pathogen, causing only insignificant number of cases, has been present in our institution since 2008.

5.5 Multiresistant *Acinetobacter*

This microorganism is responsible for 7300 infections and the death of 500 patients per year in the USA.

Compared to national and international data, the occurrence of this pathogen is rare in our hospital. The high increase in the incidence in our country from 2005 has not affected our hospital yet. We have observed only 15 cases during 5 years.

5.6 Carbapenem-resistant and carbapenemase-producing *Enterobacteriaceae*

The epidemiological situation in our hospital is good regarding these pathogens, which belong to the most dangerous group of MDRB. The 6 CRE cases detected during a 3-year period underline the possible occurrence of this problem. The use of carbapenem antibiobitics is regulated by an antibiotic protocol in our hospital.

5.7 Vancomycin-resistant *Enterococcus*

Each year in the USA, 20 000 infections and 1300 deaths are attributable to this pathogenic agent. Based on the consequences drawn from the 5 cases in our hospital, if a patient is transferred from an other healthcare factility, from which previous VRE positive cases had come, VRE screening is done on admission.

5.8 *Clostridium difficile*

250 000 infections and 14 000 deaths are due to this microbe each year in the USA. However, a 10% decline in the number of cases was achieved between 2011 and 2013.The microbe has been present in our hospital since 2008. An explosive rise of incidence in 2011, the increasing number of cases from year to year since then and the 3 outbreaks caused by 027 serotype called our attention to the fact that this pathogen is the second greatest problem in our hospital.

5.9 Surveillance at the Department of Oral and Maxillofacial Surgery

The practice of PAP is widely accepted and its HCAI reducing effect is unquestionable. The worldwide practice shows great variety ranging from a single shot to a seven-day course. However, the duration of prophylactic antibiotic use is characterized by a declining tendency. The chosen antibiotic agent should be effective against bacteria that can contaminate the surgical site. Besides, the agent should be non-toxic, bactericide, parenterally applicable and not too expensive. The antibiotic has to reach the appropriate concentration during the operation at the site of the expectable contamination. In view of this, the single shot method

seems to be insufficient for preventing HCAI in case of microsurgical operations of long duration.

Analyzing the cases of our surveillance, we found that the HCAI incidence (9.3%) appeared to be lower than the rates cited in the literature. The rates of HCAIs were comparable for primary and salvage surgery, and showed no significant differences between these two groups.

Almost all surgical interventions were categorized as belonging to group B according to the surgical wound contamination classification. We observed a rate of 8/107 (7.5%) of SSI, which fits well into this category. For salvage operations, this rate appeared to be 3/38 (7.9%). This figure is surprisingly low compared to those mentioned in the literature, although the number of our patients was relatively small.

Analyzing the primary and salvage surgeries together, it can be concluded that the frequency of HCAIs was adequately low and the PAP used was effective, although its duration was variable. According to the surgical literature, the length of PAP could be reduced even for microsurgical interventions at the Department of Head and Neck Surgery.

6. CONCLUSIONS

During the period studied, there were national guidelines only on MRSA and CDI. However, the surveillance data have definitly proved the presence of MDRB in our hospital, which justified the establishement of our own patient information leaflets and protocols regarding this topic. In January 2014, a European guideline on infection control measures for multidrug-resistant Gram-negative bacteria was published. It adresses 5 main fields: hand hygienic measures, active sreening cultures, contact precautions, environmental cleaning and antimicrobial stewardship. The principles of this guideline confirmed our MDRB protocol.

Based on the surveillance results, the purchase of new equipments for the hospital can be supported. One can give reasons for a separate disinfectant budget within the pharmaceutical budget of the hospital. In addition, it supported the necessity of introduction of screening tests.

The fact that some MDRB occurred and spread in our hospital only years after their emergence in Hungary – despite the large area provided and the high number of tranferred patients from other healthcare facilities – may indicate that the antibiotic policy and hospital hygienic rules are appropriate compared to other hospitals in our country.

The ever growing number of cases detected by MDRB surveillance suggests that the costs will rise (isolation, antibiotic therapy, etc.). Additionally, this trend points out to the increasingly difficult adherence to isolation rules in the long run, if the patients' decolonization can not be solved and the rate of incidence growth will not slow down.

In connection with the retrospective surveillance performed at the oral surgery unit, our data show that the PAP agents recommended and used according to the contamination category of the surgical site in this series of oral reconstructive surgery using microsurgical methods are adequate for both primary and salvage operations, for both soft tissue and composite soft tissue and bone defect replacements. The duration of PAP for primary surgery could be reduced in order to avoid the development of antibiotic resistances and to reduce the cost of PAP.

ACKNOWLEDGEMENTS

I thank

- my supervisor, Dr. Edit Hajdú Department of Infectology, University of Szeged for her time, support and the scientific guidance of my work;
- Dr. Mihály Svébis, director of Bács-Kiskun County Teaching Hospital, for his support of my work;
- Éva Varga, Ernő Nemes-Szabó and Zsolt Kárpáti for their assistance;
- Dr. Katalin Kristóf, Professor Dr. Gábor Cserni, Dr. Ferenc Oberna who also helped this dissertation to be born;
- last but not least, my husband Dr. István Sejben and my daughter Anita Sejben for encouraging and supporting me.