University of Szeged
Department of Anaesthesia and Intensive Care

Ph.D. thesis

RESULTS OF A LOCAL ANTIBIOTIC MANAGEMENT PROGRAM AND NATIONAL SURVEY ON ANTIMICROBIAL CONSUMPTION AND ON THE AVAILABILITY OF MICROBIOLOGY LABORATORY SERVICES ON ADULT INTENSIVE CARE UNITS IN HUNGARY

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ABBREVIATIONS

AB	Antibiotic
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CMI	Case mix index
DDD	Defined daily dose
ICU	Intensive care unit
ID	Infectious disease
IDS	Infectious disease specialist
IN	Intranet
ISF	International Sepsis Forum
LAMP	Local antibiotic management program
LOS	Length of stay
LRS	Lower respiratory sample
MB	Microbiologist
MBL	Microbiology laboratory
MDR	Multi drug resistant strain
MRCNS	Methicillin resistant coagulase-negative staphylococci
MRSA	Methycyllin Resistant Staphylococcus Aureus
P	Personal
PDD	Prescribed daily dose
QGR	Quinolone and gentamycin resistant strain
RDD	Recommended daily dose
SCCM	Society of Critical Care Medicine
sd	Standard deviation
SIRS	Systemic inflammatory response syndrome
SSI	Surgical site infection
T	Telephone
TGCR	Third-generation cephalosporin resistant strain
VAP	Ventilator-associated pneumonia
VRE	Vancomycin Resistant Enterococci
WBC	White blood cell count
WHO	World Health Organisation

PUBLICATIONS RELATED TO THE THESIS

Papers

I. **Peto Z,** Benko R, Matuz M, Csullog E, Molnar A, Hajdu E: Results of a local antibiotic management program on antibiotic use in a tertiary intensive care unit in Hungary, Infection 2008; **36:** 560-564 **IF: 1.831**

II. Benko R, Matuz M, **Peto Z,** Bogar L, Viola R, Doro P, Soos Gy, Hajdu E: Variations and determinants of antibiotic consumption in Hungarian adult intensive care units, Pharmacoepidemiology and Drug Safety (PMID:21796720) **IF: 2.527 (2009)**

III: Hajdú E, Benkő R, Matúz M, **Pető Z,** Hegedűs Á, Soós Gy, Bogár L, Nagy E: Milyen laboratóriumi háttér áll rendelkezésre az intenzív betegellátást végző osztályok számára? Orvosi Hetilap 2009; **150** (22):1037-1042

Other papers (not included to this thesis)

R Benko, M Matuz; E Hajdu, **Z Peto**, A Hegedus, L Bogar, Gy Soos. The participation of pharmacist in antibiotic related activities of Hungarian hospitals and intensive care units Acta Pharm Hung 2009; **79** (2):57-62

R Benko**,** M Matuz, P Doro, **Z Peto**, A Molnar, E Hajdu, E Nagy, J Gardi, Gy Soos. Pharmacokinetics and pharmacodynamics of levofloxacin in critically ill patients with ventilator-associated pneumonia. *Int J Antimicrob Agents* 2007; **30**(2):162-168. **IF_{2006}: 2.221**

R Benko, M Matuz, E Hajdu, P Doro, **Z Peto**, A Molnar, J Gardi, E Nagy, G Soos: Assesment of therapeutic efficacy based on levofloxaxcin plasma level measurement in intensive care unit patients *Infektológia és Klinikai Mikrobiológia* 2007, **14**(3-4): 97-103.

Abstracts

I. **Z. Peto** , E. Hajdu , R Benko , M. Matuz , Anna Molnar , E Nagy.: Results of a new infection control system in a tertiary intensive care unit in Hungary. P31 Magyar Aneszteziológiai és Intenzív Terápiás Társaság XXXIV Kongresszusa, Szeged, 2006

II. **Pető Z**, Benkő R, Matuz M, Molnár A, Hajdú E: A megváltoztatott sebészi antibiotikum profilaxis gyakorlat hatása az intenzív osztályos antibiotikum fogyásra. Magyar Infektológiai és Klinikai Mikrobiológiai Társaság 39. Kongresszusa, Pécs, 2011

III. R Benko, M Matuz, P Doro, A Nemeth, **Z Peto**, E Hajdu, L Bogar, Gy Soos.: Antibiotic related activities in intensive care units and the involvement of hospital pharmacists. 37th European Symposium on Clinical Pharmacy, Dubrovnik, Croatia, 2008 Abs: *Pharm World Sci* 31 (2): 335-336.

IV. R Benko, M Matuz, P Doro, G Martha, **Z Peto**, E Hajdu, L Bogar, Gy Soos.: Preliminary results of antibiotic use benchmarking survey in Hungarian ICUs. 37th European Symposium on Clinical Pharmacy, Dubrovnik, Croatia, 2008 Abs: *Pharm World Sci* 31 (2): 324-324.

V. Benkő R, Matúz M, Hegedűs Á, **Pető Z,** Soós Gy, Bogár L, Hajdú E: Tények és igények a hazai intenzív osztályok antibiotikum alkalmazásával kapcsolatban. Magyar Aneszteziológiai és Intenzív Terápiás Társaság XXXVI. Kongresszusa, Balatonfüred, 2008 Abs: *Aneszteziológia és Intenzív Terápia* 38,S1;EA18, 2008

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1. INTRODUCTION

With the help of antimicrobial agents the worldwide control of infectious diseases and infectious disease related mortalities had became possible. At the dawn of the antimicrobial era antibacterial agents were seen as miracle drugs but the emergence of drug-resistant organisms has impaired their therapeutic efficacy. [1-3] Microbial resistance has been known since the earliest days of antibiotic therapy but the process has rapidly accelerated during the last 20 years and is now reaching alarming levels. Increasing incidence of resistant bacteria – like Vancomycin resistant Enterococci (VRE) or Methicillin resistant *Staphylococcus Aureus* (MRSA) – pose a significant threat to hospitalised patients due to the difficulties to treat these infections. (Figure 1, Figure 2.). [4-5]

Figure 1: Increasing incidence of Vancomycin resistant Enterococci in hospitalised patients in Canada

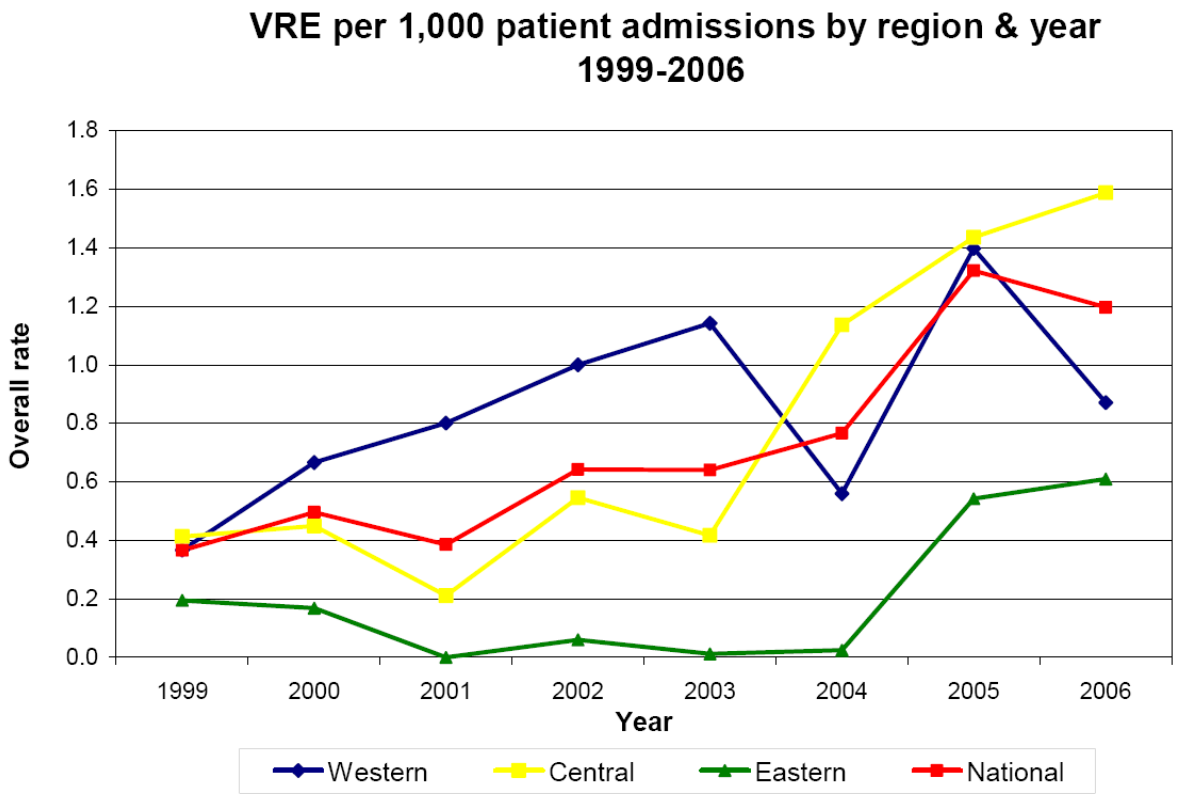
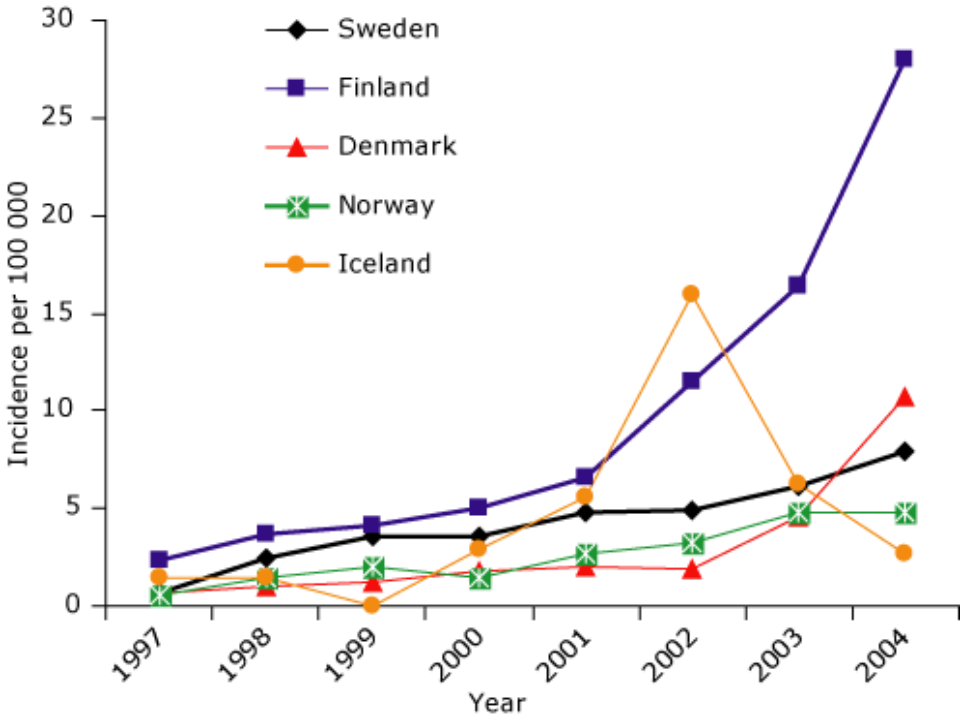


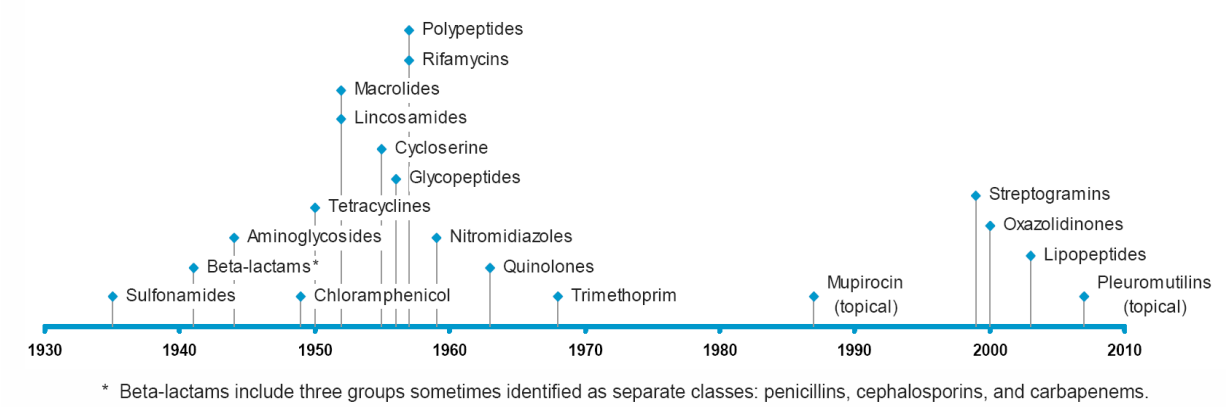
Figure 2: Incidence of MRSA reported to the national surveillance institutes in the Nordic countries from 1997-2004. Denmark, Finland, Iceland and Sweden reported infections and colonisations; Norway only reported infections.



Before the widespread introduction of antibiotics microorganisms showed almost complete sensitivity once intrinsic resistance was excluded. Organisms with intrinsic resistance are often of low virulence – like *Pseudomonas* or *Acinetobacter* spp - but they easily become a problem in immunocompromised patients managed in selection pressure environments such as intensive care units (ICU). [6]

In parallel with increasing antimicrobial resistance the development of new classes of antimocrobials has slowed down: 14 classes of new antimicrobials have been introduced between 1935 and 1968 and only five since (Figure 3). [7]

Figure 3: Discovery of different classes of antimicrobials



The development of antimicrobial resistance has become a special issue on ICUs. [5] Frequent – and often inadequate - antibiotic use, use of invasive procedures and immunosuppressed patients are not uncommon on these units, therefore ICUs are the epicentres of antibiotic use and the emergence of antibiotic resistant pathogens. [6-7] ICU patients are more likely to be exposed to antimicrobial agents before admitted to ICU and they are also more likely to be colonized with an antimicrobial-resistant pathogen from previous healthcare treatment. Colonization of ICU patients with antimicrobial-resistant pathogens can lead to infection as the patients are susceptible to hospital-acquired infection as the normal skin and mucosal barriers are compromised by the use of invasive devices. All of these factors - especially previous or inadequate antibacterial therapy - contribute to the increased risk of developing hospital acquired infections with antimicrobial resistant pathogens. [8-12]

Inadequate antimicrobial therapy involves the use of antimicrobials with poor or no in vitro activity against the microorganisms causing infection. Previous studies have shown strong association between inadequate antibimicrobial treatment and increased in-hospital mortality rates for patients with ventilator-associated pneumonia (VAP). [13-16]

To control the rise in antimicrobial resistance, various strategies have been tried and measured and regular monitoring of antibiotic use was found to be one of the most effective elements to control resistance to antibiotics. [17] Antibiotic usage monitoring should be always part of the local antibiotic policy aiming to reduce inappropriate antibiotic use, avoid antibiotic resistance and improve patient outcome. [18-20]

Antimicrobial agents have one more considerable aspect: antibiotics are one of the most frequently used - and one of the most expensive - drugs on ICU. The inappropriate use of antimicrobial agents has medical, economic and public health consequences therefore substantial efforts are needed to rationalise the antibiotic prescription practice on the ICU.

ICUs admit large number of postoperative patients from various surgical units therefore the appropriateness of the surgical antimicrobial prophylaxis is very important in order to keep antimicrobial drug usage, resistance and cost in bay. For surgical antimicrobial prophylaxis antimicrobials are given to prevent surgical site infections (SSI). SSI is an important outcome measure for surgical procedures and the term SSI is used to encompass the surgical wound and infections involving the body cavity, bones, joints, meninges and other tissues involved in the operation. In procedures that require the insertion of implants or prosthetic devices the term also encompasses infections associated with these devices. The goals of prophylactic administration of antibiotics to surgical patients are to reduce the incidence of SSI, to minimise adverse events including the effect of antimicrobials on the patient's normal bacterial flora and to cause no or minimal change to the patient's host defences.

The appropriate antimicrobial prophylaxis is one crucial component of an effective antibiotic stewardship policy to control healthcare associated infections. It should not stand alone and other means – such as proper patient preparation including identifying and treating infections remote to the surgical site before surgery, blood glucose level control, preoperative chlorhexidine bath of the patient, appropriate skin preparation for both the surgeon's hands and the surgical site, etc. – should also be done to minimize the risk of SSI.

By definition one must be able to differentiate the prophylactic antimicrobial treatment from the therapeutic antimicrobial treatment. Prophylactic antimicrobial treatment is the use of antibiotics before, during, or after a diagnostic, therapeutic, or surgical procedure to prevent infectious complications. Therapeutic antimicrobial treatment is use of substances that reduce the growth or reproduction of bacteria, including eradication therapy. This term is used to describe antimicrobial therapy prescribed to clear infection by an organism or to clear an organism that is colonising a patient but is not causing infection. [21]

To achieve a succesful, evidence based antimicrobial usage on ICU there is a need for a well planned and executed antimicrobial management (or as known antibiotic stewardship) program. In this Ph.D. work I have aimed to evaluate the impact of a new local antibiotic management program (LAMP) on antibiotic usage on the Intensive Care Unit II. of the Department of Anaesthesia and Intensive Care, University of Szeged, Hungary.

With the antimicrobial consumption data from this ICU I was able to examine my results in context with the comprehensive antibiotic use and microbiology service availability data from Hungarian adult ICUs.

2. BACKGROUND

2.1. Antibiotic stewardship

Antimicrobial stewardships programs generally refer to an ongoing organised program to improve antimicrobial use at a health care system to improve patient outcomes and cost-effectiveness and to reduce antimicrobial resistance at the same time. To achieve this goal antimicrobial stewardship programs may employ different tools and activities as the followings: [22]

1. Education: Creation of guidelines for antimicrobial use by antimicrobial committee to change antibiotic prescription patterns and habits amongst physicians. The advantage of this approach is the possibility of using the power of active education to improve practice and to accept changes without the loss of the prescriber's autonomy. The education should be intense enough to achieve the desired effect on clinicians.
2. Formulary/restriction: This approach restricts dispensing of targeted antimicrobials and seeks approval from an authority to prescribe certain antimicrobials. This is the most direct control over antibiotic use and it potentially leads to perceived loss of autonomy by prescribers. Out of hours personnel cover is required for approvals.
3. Review and feedback: With this approach the appropriateness of antimicrobial therapy is reviewed and discussed daily with clinicians, pharmacists and infection control specialists. High degree of co-operation is required to maintain effectivity and compliance with recommendations is voluntary.
4. Computer assistance: With the help of the computerised decision system it is possible to provide up-to-date patient specific data at the point of care and to make patient-specific recommendations. This approach needs significant resources invested to build up, validate and maintain the system.
5. Antimicrobial cycling: This approach includes the scheduled rotation of antimicrobials driven by the antimicrobial comittee. It may reduce resistance by changing selective pressure. It is not easy to ensure compliance with the cycling protocol and there are concerns about the effectiveness of the cycling.

6. Other: temporary local efforts like switching antimicrobials in the same class for cost-saving purposes, intravenous-to-oral switching programs and pharmacokinetic consultation services may all have impact on antimicrobial use but these steps are less likely to have a significant impact on global antimicrobial use or antimicrobial resistance.

The presence and the impact of different antimicrobial stewardship programs were studied previously: a study from 88 United States hospitals found that two-thirds had an antimicrobial formulary and teaching hospitals tended to be more likely to have antimicrobial restriction programs. [23, 24] This may be because of the admittance of sicker patients, higher need for antimicrobial control and more available resources. Another study conducted by Centers for Disease Control and Prevention's Project (ICARE) showed that all participating 47 hospitals used an antibiotic formulary, and 91% utilised at least one other antimicrobial stewardship strategy. [25]

A recent review – pro/con debate – concluded that all ICUs should have an antimicrobial stewardship program accompanied by a system to monitor clinical outcomes such as mortality and length of stay. This system presents an excellent opportunity for infection control and other patient quality and safety initiatives. Close collaboration between intensive care physicians, infectious disease and infection control specialists, microbiology services and pharmacy are needed for the success of an antimicrobial stewardship program. [26]

2.2 Concept of the defined daily dose (DDD) and the Anatomical Therapeutic Chemical (ATC) classification system

The DDD is an internationally accepted technical unit in drug utilisation studies. The purpose of the ATC-DDD system is to serve as a tool for drug utilization research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels.

The DDD means the assumed average maintenance dose per day for a drug used for its main indication in adults but one should know that the DDD does not necessarily correspond to the recommended-, or actually prescribed daily dose (RDD and PDD). The World Health Organisation (WHO) recommends the use of the number of DDDs per 100 patient-days in hospitals settings as the standard technical unit. The ATC and DDD system are revisited and changed sometimes therefore it is important to know the version of the ATC index is used in drug utilisation studies.

In the ATC classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels and a seven digit code identifies each active substance (Table 1). The drugs are divided into fourteen main groups (1st level), with pharmacological/therapeutic subgroups (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups. The ATC coding and DDD of commercially available penicillins in Hungary are shown in Table 1.

Table 1: ATC coding and DDD of commercially available penicillins in Hungary

ATC code 3	**ATC code 5**	**Drug**	**Trade name**	**DDD oral (g)**	**DDD parenteral (g)**
J01CA	J01CA01	ampicillin	Semicillin	2	2
	J01CA04	amoxicillin	Amoxicillin		
J01CE	J01CE01	benzylpenicilline potassium	Penicillin G		3,60
	J01CE02	phenoxymethylpenicillin	Ospen	2	
	J01CE06	penamecillin	Maripen	1,05	
	J01CE09	benzylpenicillin-procain	Retardillin		0,6
J01CF	J01CF01	dicloxacillin	Novapen	2	2
	J01CF02	cloxacillin	Orbenin	2	2
	J01CF03	meticillin	Celbenin		4
	J01CF04	oxacillin	Infectostaph	2	2
	J01CF05	flucloxacillin	Staphylex	2	2
J01CR	J01CR01	ampicillin, sulbactam	Unasyn		
	J01CR02	amoxicillin+clavulanic acid	Augmentin	1	3
	J01CR04	sultamicillin	Unasyn	2	2
	J01CR05	piperacillin+tazobactam	Tazocin		14

Antibiotics in J01CF group are not marketed in Hungary.

2.3 The role of the microbiology laboratory services

Clinicians treating life threatening infections expect quick and accurate information from microbiology laboratory services. Customer satisfaction has been reported as a critical performance measure for clinical microbiology laboratory medicine. Accuracy of results and physicians rated turnaround times are the most important service aspect for clinical laboratories. [28, 29] The turnaround time is the time elapsed between the arrival of a given microbiology sample to the laboratory and the microbiology report received by the clinician.

The quality of the microbiology services plays a vital role especially in ICUs and in the Surviving Sepsis Campaign. The Surviving Sepsis Campaign - started by by the European Society of Intensive Care Medicine, International Sepsis Forum and Society of Critical Care Medicine - is aimed to improve the diagnosis, survival, and management of patients with sepsis. The so called “Bundles” have been designed to allow teams to follow the proper timing, right sequence, and goals to achieve a 25 percent reduction in mortality due to severe sepsis or septic shock. [30] In the initial Sepsis Resuscitation Bundle the second element is to obtain blood cultures prior to antibiotic administration to identify the organism that caused severe sepsis and the samples are sent to the microbiology laboratory together with a request form. Microbiology laboratory assistants process the sample according to the laboratory algorithms, they perform microscopy and culture to identify potential pathogens and establish antimicrobial susceptibilities. When all results are complete, the clinical microbiologist performs an authorisation and the report is to be sent to the requesting clinician. The turnaround time of the microbial samples is an important issue: as soon as the intensive care specialist knows the detailed description of the microorganism responsible for a given infection the tailored antimicrobial therapy could be started.

The choice of antimicrobials should be guided by the susceptibility of likely pathogens in the given community and hospital. The regimen should cover all likely pathogens since failure to initiate appropriate therapy promptly has adverse consequences on outcome. [31-33] The antimicrobial regimen should always be reassessed after 48–72 hours on the basis of microbiological and clinical data to prevent the development of resistance, to reduce toxicity and costs. For that reasons the availability of an integrated, well equipped and properly staffed microbiology laboratory services is vital. A microbiology laboratory - as part of the hospital diagnostic services - is an important tool for infection control and ideally it should be working every day on a 24 hour basis. Microbiology laboratories have three main functions:

- the diagnosis of infection in an individual patient
- to support the hospital’s infection prevention and control program

- to provide resistance and surveillance data for the wards and the hospital to support empirical antimicrobial selection by the physicians.

The good co-operation between intensive care physicians, infection control specialists and microbiology laboratory specialist is paramount since if the etiological diagnosis of infection is rapid and accurate, the patient will be treated properly at the beginning of infection and the outcome is more promising. [34] A study on the clinical implications of increasing antimicrobial resistance in patient isolates from a leading medical center world included the statement that "Effective surveillance (for resistance identification and control) depends on a fully equipped, efficient, and accurate microbiology laboratory that maintains close contact with clinicians". [35]

3. MAIN RESEARCH OBJECTIVES

1. To evaluate the impact of the new local antibiotic management program on antibiotic usage introduced on the Intensive Care Unit II. of the Department of Anaesthesia and Intensive Care, University of Szeged, Hungary.

2. To investigate the impact of the revised surgical antimicrobial prophylaxis management program on the antimicrobial consumption on the same ICU.

3. To present the results of a national survey on antimicrobial consumption and on the availability of microbiology laboratory services on adult surgical intensive care units benchmarked against the Intensive Care Unit II. of the Department of Anaesthesia and Intensive Care, University of Szeged, Hungary.

4. METHODS AND MATERIAL

4.1. Local antibiotic management program

The study was conducted on the six-bed special surgical ICU of the University of Szeged. The unit was a tertiary referral center responsible for the treatment of critically ill neurosurgical, trauma and orthopaedic patients from south Hungary. Other cases, e.g. general surgical and medical patients, were transferred to other facilities for expert care after stabilization and/or resuscitation. The following data was obtained on yearly or monthly basis for 3 years before (2000–2002) and after (2003–2005) the implementation of the new antibiotic management program:

(1) Patient data – number of patients, age, type of primary disease (neurosurgical, trauma, orthopedic surgery related, medical or general surgical), ICU outcome (survival or death), length of ICU stay (LOS) in days and the case mix index (CMI) - were collected. All of these data were extracted from electronic reports, provided by the Financial Department of the University of Szeged, Hungary.

(2) Infection data – number and aetiologic agents of bloodstream infections - was collected. Bloodstream infections were defined as sepsis with documented bacteraemia. Sepsis was diagnosed in accordance with the American College of Chest Physicians/ Society of Critical Care Medicine consensus conference agreement. [36]

To detect the possible infections two or three pairs of blood cultures (central venous line, venepuncture, arterial line) were taken from each patient presenting with the symptoms of systemic inflammatory response syndrome (SIRS). Bacteraemia was confirmed when at least one blood culture was positive for a pathogenic bacterium; or two blood cultures (one from venepuncture) were positive for common skin bacteria.

During 2000–2003, the VITAL system (bioMerieux, L'Etoile, France) was used, but from 2004 the BACTEC9000 (Beckton Dickinson Diagnostics, Franklin Lakes, NJ, USA) blood culturing system was utilized. Species identification was performed with either the Vitek 2 (bioMerieux, L'Etoile, France) identification automat or conventional biochemical methods as required. Susceptibility to relevant antibiotics was tested using the disk diffusion technique according to the standards of the Clinical and Laboratory Standards Institute (CLSI) [37]. Duplicate isolates from the same patients with identical susceptibility patterns were excluded. Clinical findings were retrieved from patient charts, while microbiological data were obtained from the database of the Institute of Clinical Microbiology.

(3) Antibiotic consumption data. The monthly number of antibacterial packages dispensed to the intensive care unit was obtained from the Central Pharmacy. Consumption data

of systemic antibacterials were calculated according to the 2005 version of the WHO ATC-DDD methodology, and expressed as DDD per 100 patient-days.

Before November 2002, there were no restrictions on the prescription of antibiotics and an infectious disease (ID) specialist was not involved in the clinical decision-making. The ICU was covered by intensive care physicians on an on-call basis therefore there was no nominated critical care physician. Antimicrobial drugs could be started, changed and stopped without consultation with infectious disease specialist and junior doctors could alone decide on antibiotic therapy. On the ICU there were no data collected on antimicrobial drug consumption or unit level antimicrobial resistance.

In November 2002, the new local antibiotic management program was implemented with the following two main pillars:

(a) An ICU consultant/ID specialist consultation system was implemented. A nominated ID specialist/microbiologist performed a daily bedside consultation five days a week and further provided 24 h telephone support seven days a week.

(b) Intensive care consultant physician post was created and the ICU was supervised by four senior anaethetist consultants in monthly rotation. They lead the unit and follow all patients seven days a week. Apart from other responsibilities the prescription, or change in the prescription of antibiotics was restricted to the four dedicated ICU consultants, after consultation with the ID had occurred.

To measure the impact of the local antibiotic management program on antibiotic use we applied segmented regression analysis of interrupted time-series as proposed by Ramsay et al. [38] Normality was tested by Shapiro-Wilk test while autocorrelation by the Durbin-Watson test. Detailed description of the method and its application are available in previous papers. [39, 40] Differences in patient and ICU data were tested by the Chi-square, Fischer's exact or the independent t-test, as appropriate. All statistical analysis was performed with the SPSS program package (version 15). A p-value less than 0.05 were considered statistically significant.

4.2. Revised surgical antimicrobial prophylaxis management program

While evaluating the results of the local antibiotic management program a suspiciously high second generation cephalosporin consumption was found. As these drugs – mainly cefuroxim – were used almost solely for SSI prevention and antibiotics for surgical prophylaxis were administered on the request of surgeons it was logical to revise the SSI prophylaxis practice on the ICU. The characteristics of the unit otherwise remained the same as mentioned above but by the time of the study the number of the ICU beds were increased to eight from six. The patient and antimicrobial consumption data obtained on yearly and monthly basis for three

years before (2003–2005) and four after (2006–2009) the implementation of the new antibiotic prophylaxis policy were the same collected for the first study. All of these data were extracted from electronic reports, provided by the Financial Department of the University and Central Pharmacy. Consumption data of systemic antibacterials were calculated according to the newer 2009 version of the WHO ATC-DDD methodology, and expressed as DDD per 100 patient-days.

With the implementation of the new antibiotic prophylaxis management in January 2006 the four intensive care supervising consultant covering the ICU in monthly rotation – who were responsible for all antimicrobial therapy on the ICU as well – took over the responsibility for the surgical prophylaxis. Before this intervention surgeons precribed the antimicrobial prophylaxis for surgical patients both in the theatre and on the ICU thereafter. Even though the institutional surgical antimicrobial prophylaxis guideline was clear about the choice of the antibiotics and the length of the prophylaxis the recommendations were not always followed. After the intervention the prophylaxis was stricktly given according to the University of Szeged's antimicrobial prophylaxis guideline: cefuroxime was recommended as the main agent and on the ICU the prophylaxis was automatically discontinued within 24 hours after the surgery (automatic stop order). These two novel elements were the backbone of the new surgical prophylaxis management programme.

Only carefully selected patients – patients with extensively contaminated open wounds or major abdominal trauma patients after laparotomy - received additional metronidazole cover. For major abdominal surgery third generation cephalosporine and metronidazol was given for surgical prophylaxis according to the institutional guideline and – contrary to the pre-intervention years - the antibiotics were discontinued within the 24 hours period after the surgery. In case of beta-lactame hypersensitivity the patient received clindamycin or vancomycin if the patient was high risk for MRSA infection. To measure the impact of the new antibiotic prophylaxis management on antibiotic use we applied the same statistical tests we have used previously to evaluate the results of the local antibiotic management program.

4.3. National survey on antimicrobial consumption and on the availability of microbiology laboratory services on adult intensive care units in Hungary

In 2007, the 110 adult Hungarian ICUs were repeatedly addressed by our research group to provide data on different antibiotic related measures (activity of the local antimicrobial committee, existence of local guidelines and policies), availability of microbiologic services, unit data and patient characteristics from 2006. The ICUs had received a detailed (97 question) questionnaire by mail and in electronic format. The answering ICUs' hospital pharmacies were contacted than to provide package level antibiotic use data dispensed during 2006. Crude package level data was converted into DDDs and expressed as DDD per 100 patient-days. For each ICU antibacterials were ranked by volume of DDDs and the number of antibacterials which were accounted for 90% of total antibiotic use (DU90% segment) was noted.

Hospital specific antibiotics were defined as third- and fourth-generation cephalosporins, carbapenems, and aminoglycosides. The antibiotic usage and patient turnover data were validated and outliers and unexpected values were identified by a query answered by the head of the given ICU and central pharmacy departments. ICUs were categorized according to the provided level of care (local, regional, tertiary care) and they were classified to be surgical, medical or interdisciplinary based on the treated patient mix. The relationship between antibiotic use in surgical ICUs and potential influencing factors – i.e. CMI and LOS- were also examined.

The CMI is an economic parameter calculated using diagnoses-related groups and shows the severity of the illnesses (higher index means more complicated cases treated) and serves as a basis for the unit/hospital reimbursement. [41]

The correlation between the antimicrobial use and the CMI and LOS of the surgical ICUs was investigated with Pearson correlation analysis.

Questions No. 42 – No. 67 of the same 97-question survey collected information about the availability of the microbiology laboratory services and the infectious disease specialist/microbiologist consultation options for intensive care units in Hungary. There were questions about the local microbiology laboratory's office hours, the out-of-hours activity, and the turnaround time of the specimens. Microbiology and infectious disease consultation opportunities and availability were questioned as well. The questionnaire is shown in Appendix 1.

5. RESULTS

5.1. Local antibiotic management program

Patient and ICU data before (2000-2002) and after (2003-2005) the introduction of the local antibiotic management program are summarized in Table 2.

Table 2: Patient and ICU data before and after the introduction of the local antibiotic management program

Patient and ICU data	200-2002	2003 - 2005	p value
Total number of patients	1646	1757	
Number of patients with primary disease:			
Neurosurgical	1059 (64.4%)	1123 (63.9%)	
Trauma	298 (18.1%)	366 (20.8%)	0.006*
Orthopedic related surgery	249 (15.1 %)	209 (11.9%)	
Medical or general surgical	40 (2.4 %)	59 (3.4%)	
Mean age (years) ± sd	56.3 ± 17.2	56.8 ± 17.6	0.401**
ICU mortality/1000 patients	66.2	64.3	0.440**
Mean length of stay (days) ± sd	2.6± 4.7	2.4± 3.8	0.214**
Mean Case Mix Index ± sd	6.3 ± 1.5	6.0 ± 0.7	0.258**

sd: standard deviation, *: significant, **: non significant, +: Local Antibiotic Management Program

There were no significant differences in the mean age of patients or ICU mortality rate between the two periods. The mean length of stay showed a moderate, but statistically insignificant decrease. The CMI also did not differ significantly before and after the intervention. However, although the primary admission diagnoses did show statistically significant differences before and after the implementation of the local antibiotic management program, we did not consider these differences clinically relevant (e.g. 3.2% decrease in the relative number of orthopedic surgery related patients).

There was no significant difference in the distribution of pathogens and in the antimicrobial resistance in the two periods.

The distribution of pathogens of bloodstream infections before and after the introduction of the local antibiotic management program is listed in Table 3.

Table 3: The distribution of pathogens of bloodstream infections before and after the the introduction of the local antibiotic management program

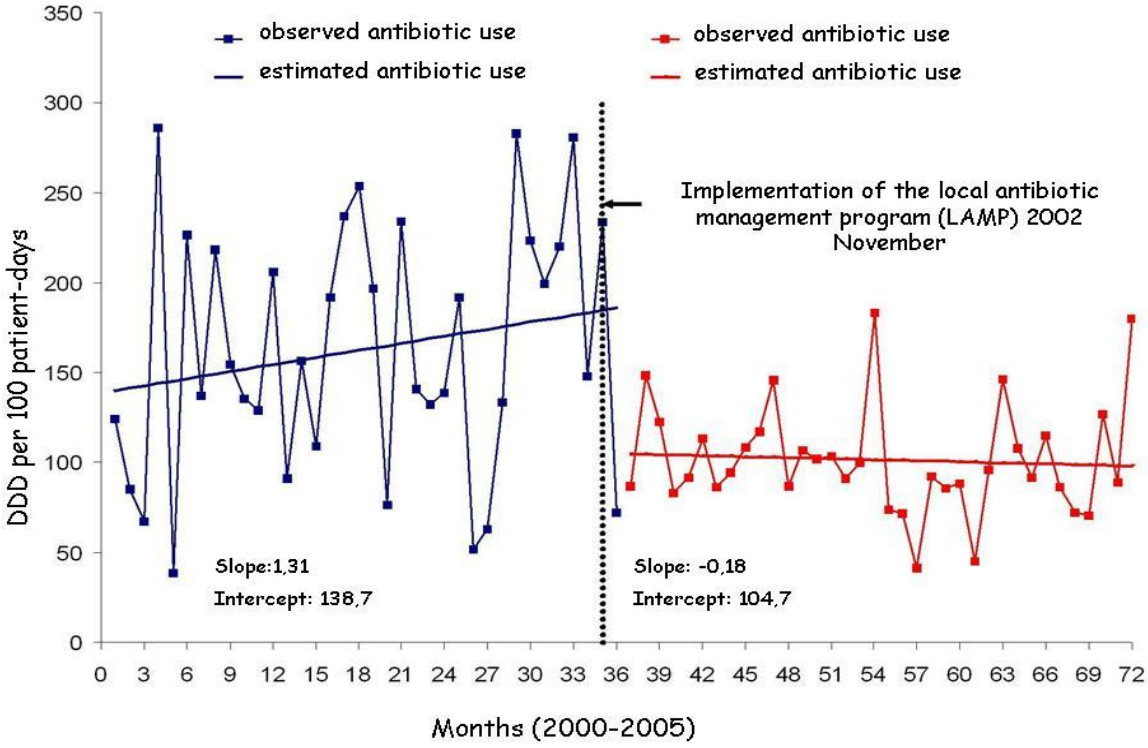
Pathogens of bloodstream infections	**2000-2002**	**2003-2005**
Staphylococcus aureus/MRSA	10/1	11/4
Coagulase-negative staphylococci/MRCNS	1/1	2/2
Streptococcus pneumoniae	1	0
Streptococcus spp.	1	1
*Enterococcus faecalis/*VRE	9/0	9/0
Bacillus cereus	1	2
Corynebacterium jejkeum	1	0
Escherichia coli/TGCR	3/0	5/0
Klebsiella pneumoniae/ TGCR	8/0	7/0
Enterobacter spp./ TGCR	4/0	4/0
Citrobacter koseri	0	1
Pseudomonas aeruginosa/MDR	5/2	3/0
Pseudomonas spp.	2	1
*Acinetobacter baumannii/*QGR	3/0	3/0
Stenotrophomonas maltophilia	0	1
Fusobacterium necrogenes	1	0
Actinomyces meyeri	0	1
Candida spp.	2	0
Total number of isolated bacteria	52	51
Total number of bloodstream infections	40	44

MRSA: methicillin resistant *Staphylococcus aureus;* MRCNS*:* methicillin resistant coagulase-negative staphylococci*;*VRE Vancomycin resistant *Enterococcus faecalis*; TGCR: third-generation cephalosporin resistant strain; MDR: Multi drug resistant strain (resistant to at least three antipseudomonas antibiotics); QGR: quinolone and gentamicin resistant strain

The total number of the microbiologically confirmed bloodstream infections was similar in the two periods (40 vs 44). The most frequently isolated microorganisms were the same in both periods with *Staphylococcus aureus* the most common isolate. Strains with emerging resistance mechanisms rarely occurred in both periods among the blood culture isolates (Table 4). Only MRSA strains were more frequently seen after the implementation of local antibiotic management program but the numbers of the confirmed MRSA bloodstream infections were so low – only four in three years - that were considered them to be sporadic cases (Table 4).

The segmented regression analysis revealed that the estimated mean antibiotic consumption decreased significantly to 101.3 DDD per 100 patient-days (95% CI: 100.7–102.0) from 162.9 DDD per 100 patient-days (95% CI: 158.3–167.6) after the introduction of the local antibiotic management program. The estimated mean change in slope of the time series was 1.5 (95% CI: –0.16 to –2.83) DDD per 100 patient-days per month. The graphic illustration of segmented regression analysis of interrupted time-series data and further predictions for reductions in antibiotic use are shown in Figure 4.

Figure 4: Segmented regression analysis of interrupted time-series data before and after the implementation of the new local antibiotic management program and further prediction for reductions in antibiotic use



The decrease in antibiotic use is attributable to the significant drop in the consumption of quinolones, aminoglycosides, glycopeptides, metronidazole, and carbepenems (Table 4).

Table 4: Usage data (expressed in DDD per 100 patient days) of main antibiotic groups before and after the introduction of the local antibiotic management program.

Antibiotic use in DDD per 100 patient days	**2000-2002**	**2003-2005**	**% change**
Tetracyclines	0.14	0.19	35.5
Penicillins	21.6	14.1	-34.8
Cephalosporins	41.4	47.0	13.5
Carbapenems	18.5	9.9	-46.6
Sulfonamides and trimethoprim	0.0	0.1	*na
Macrolides and lincosamides	6.7	3.8	-42.6
Aminoglycosides	7.7	1.0	-86.9
Fluoroquinolones	21.1	11.2	-46.9
Glycopeptides	25.7	6.4	-75.1
Imidazoles	11.7	5.5	-53.3

Amongst the cephalosporins the third generation cephalosporin use was halved (11.0 vs 6.1 DDD per 100 patient-days) whilest an increase in the usage of second generation cephalosporins was detected (29.5 vs 39.1 DDD per 100 patient-days). Cefuroxime was the most commonly used antibiotic in both periods. The second and third most used agents were vancomycin (20.2 DDD per 100 patient-days) and ciprofloxacin (13.0 DDD per 100 patient-days) before and amoxicillin–clavulanic acid combination (9.3 DDD per 100 patient-days) and meropenem (7.7 DDD per 100 patient-days) after the policy. Oral products were used only marginally on the unit in both periods (6.9%vs 4.4%).

5.2. Revised surgical antimicrobial prophylaxis program

Patient demographics, ICU descriptives and antibiotic usage data are summarized in Table 5.

Table 5: Patient and ICU data (Part A) and antimicrobial use in DDD/100 patient days (Part B) before and after the implementation of the surgical prophylaxis policy

Part A

Patient and ICU data	**2003-2005**	**2006-2009**	**P-value**
Total number of patients	1757	3459	
Male (%)	846 (48.2%)	1702 (49.2%)	0.482
Number of patients with primary disease (%)			<0.001
Neurosurgical	1123 (63.9%)	2250 (65.0%)	
Medical or general surgical	59 (3.4%)	116(3.4%)	
Orthopedic related surgery	209 (11.9%)	278 (8.0%)	
Trauma	366 (20.8%)	815(23.6%)	
Mean age (years) ± sd	56.8 ± 17.6	59.2 ± 17.6	<0.001
ICU mortality per 1,000 patients	64.3	62.7	0.857
Mean length of stay (days) ± sd	2.4 ± 3.8	2.2 ± 3.2	0.062
Mean CMI ± sd	6.0 ± 0.7	6.1 ± 1.1	0.942

Part B

Antibiotic use in DDD/100 patient days	**2003-2005**	**2006-2009**	**% change**
Penicillin combinations with beta-lactamase inhibitors	13.81	13.81	-0.02
Second generation cephalosporins (cefuroxime)	39.07	32.62	-16.50
Third generation cephalosporins	6.10	3.62	-40.71
Carbapenems	9.88	9.38	-5.04
Lincosamides (clindamycin)	2.68	3.24	21.05
Fluoroquinolones	11.19	13.65	22.04
Glycopeptides (vancomycin)	6.40	2.83	-55.82
Imidazoles (metronidazole)	5.48	3.54	-35.48

sd: standard deviation, CMI: Case mix index

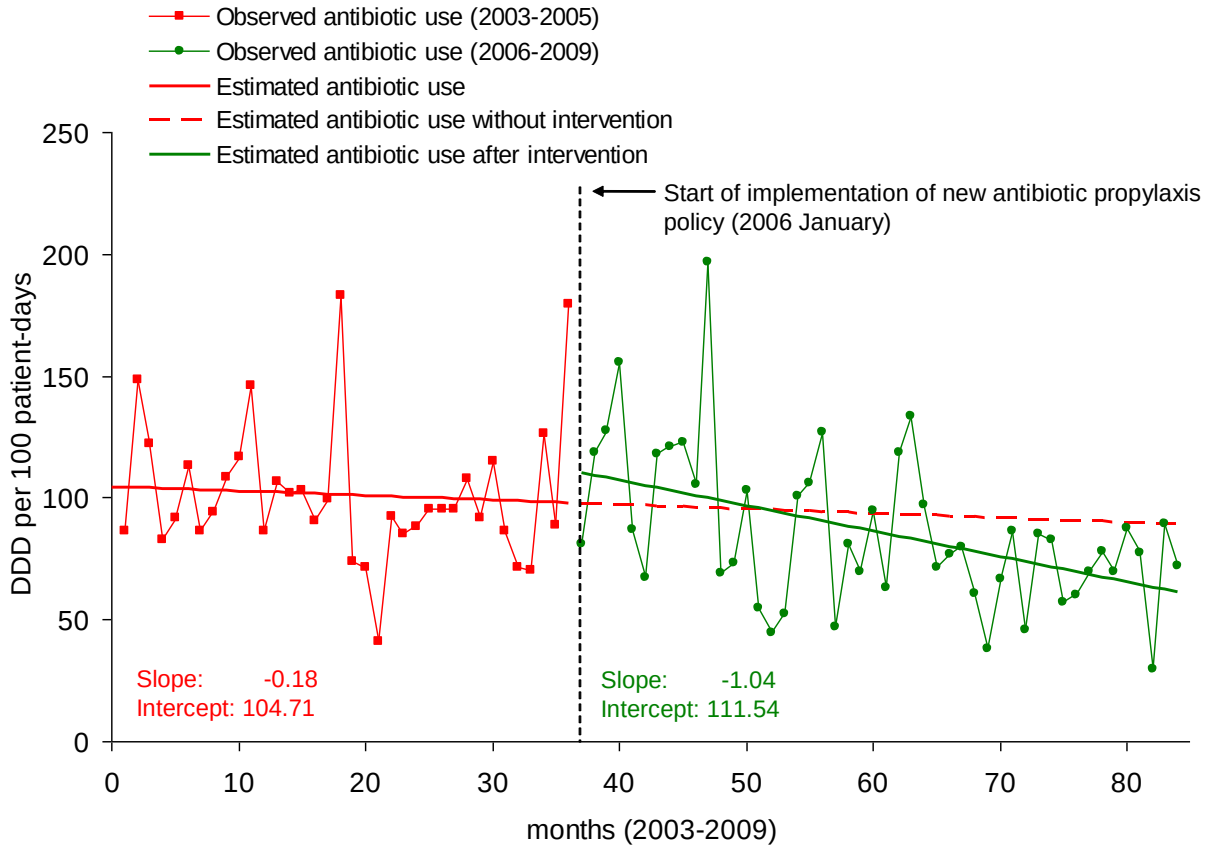
The significant difference in the primary admission diagnoses was due to the smaller number of ortopedic patients but it was not considered clinically relevant. There were no significant differences in the mean length of stay, the CMI and the ICU mortality rate between the two periods. As the number of financed ICU beds increased from six to eight in 2006 the number of patients treated on our ICU was significantly higher in the second period. The mean age of the patients increased but since it is a natural phenomenon we did not consider this clinically important

The changes in the consumption of main antibiotic subclasses are summarized in Table 5 Part B.

The decrease in antibiotic use was mainly attributable to the drop in the consumption of cefuroxime. This agent was the only second generation cephalosporin used at the unit and its use was reserved for surgical prophylaxis. However in 2006 – in the transient year – cefuroxime had outstanding use (51.8 DDD per 100 patient-days), thereafter in the three consecutive years a continuous and significant decrease (36.42 – 28.1 – 18.8 DDD per 100 patient days) was observed in parallel with the inclusion of more and more patients in the new policy. Other agents used for surgical prophylaxis before and/or after the intervention like third generation

cephalosporins, metronidazole and vancomycin also exhibited a significant drop in their use. The clindamycin and fluoroquinolon use increased in the second period. The graphic illustration of segmented regression analysis of interrupted time-series data and further predictions for reductions in the antibiotic use are shown in Figure 5.

Figure 5: Segmented regression analysis of interrupted time-series data before and after the implementation of the new antibiotic prophylaxis policy and further prediction for reductions in antibiotic use



The segmented regression analysis revealed that the estimated mean antibiotic consumption decreased significantly from 101.3 DDD per 100 patient-days (95% CI: 100.7–102.0) to 86.0 DDD per 100 patient-days (95% CI: 81.1–90.9) after the introduction of the new antimicrobial prophylaxis policy, which corresponds to a 15% decrease in total use. The estimated mean change in the slope of the time-series was - 0.89 DDD per 100 patient-days per month (95% CI: -0.47 to -1.3).

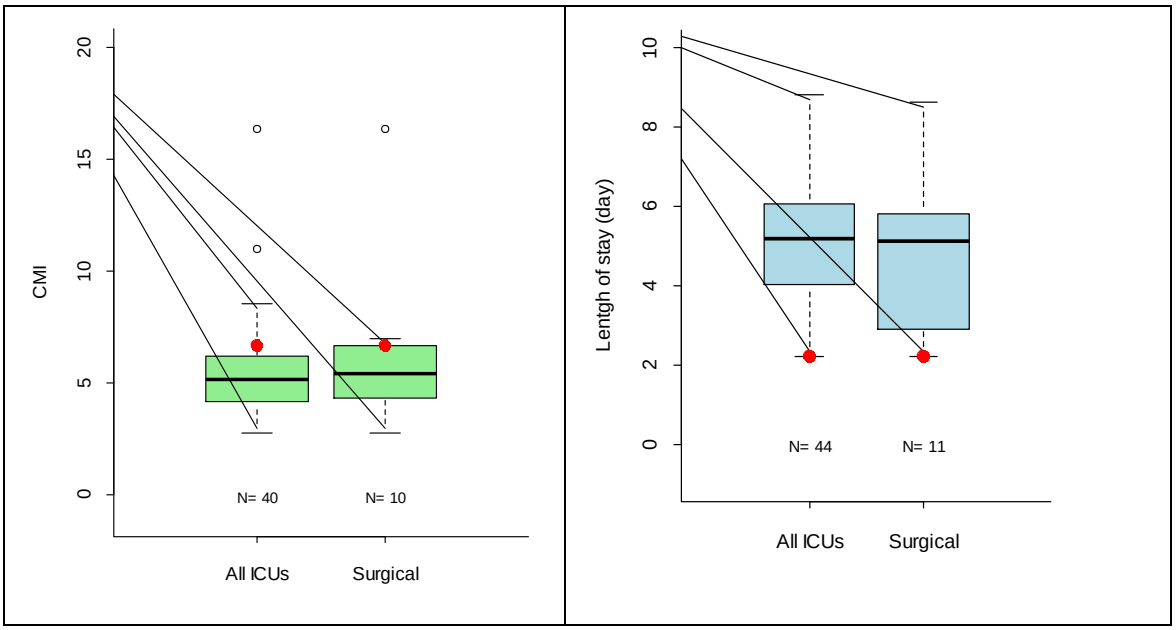
5.3. National survey on antimicrobial consumption and on the availability of microbiology laboratory services on adult intensive care units in Hungary

49 units provided antimicrobial consumption data but during the validation process five ICUs were excluded due to missing/invalid data.

A total of 92 476 DDDs, 95 086 patient-days and 19 590 admissions were included in the analysis from the 7 tertiary care, 14 regional and 23 local ICUs. ICUs were categorised as surgical (n=11), medical (n=8) and interdisciplinary (n=25) based on the treated patient mix.

The median number of beds per ICU was eight (range 6–22) and the mean number of admissions per ICU was 445 (range 129–1038) in 2006. The case mix index ranged between 2.8 and 16.3 with a median of 5.2. Mean (± standard deviation) length of stay was 5.3±1.7 days. The CMI and the LOS of the surveyed ICUs can be seen on Figure 6.

Figure 6: The CMI and the LOS of the surveyed ICUs. Red dots indicate the position of our ICU.

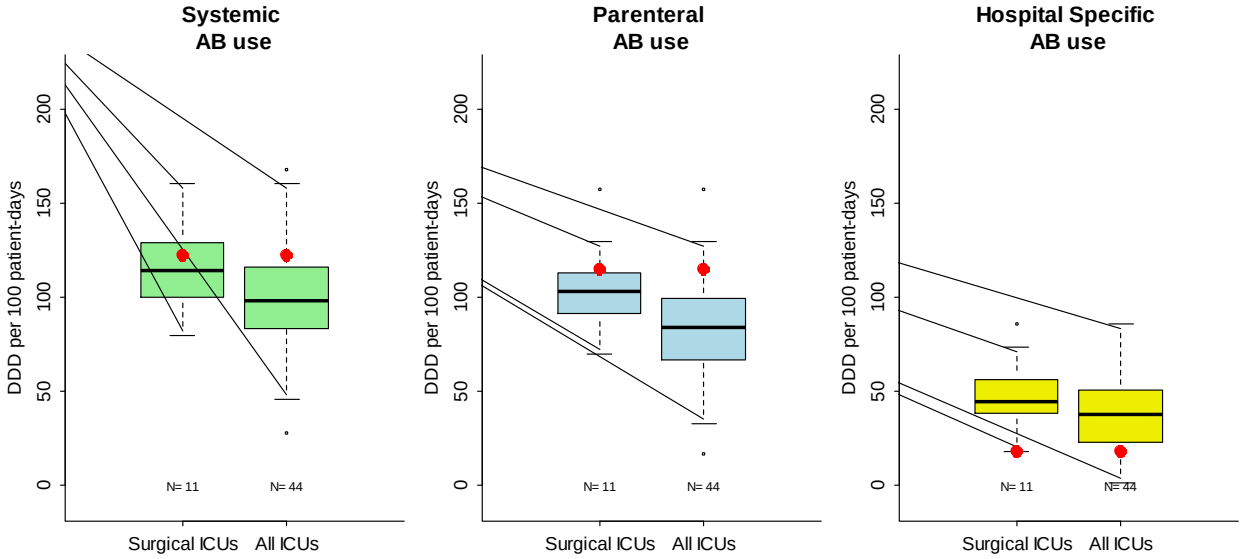


CMI: case mix index, LOS: length of stay

Considering all participating ICUs (N=44) the consumption of systemic antibacterials was between 27.9 and 167.8 DDD per 100 patient-days and with a median of 97.7 and mean of 98.7 DDD per 100 patient-days.

Figure 7. showes the systemic, the parenteral and the hospital specific antibiotic use on the surveyed ICUs.

Figure 7: The systemic, the parenteral and the hospital specific antibiotic use on the surveyed ICUs. Red dots indicate the position of our ICU.



Hospital specific AB: third- and fourth-generation cephalosporins, carbapenems, aminoglycosides, and glycopeptides

On our ICU the systemic and the parenteral AB use was higher than the median of the surgical and the all surveyed ICUs. The hospital specific AB use was less than the median of the all surveyed ICUs and it was the lowest amongst the surgical ICUs.

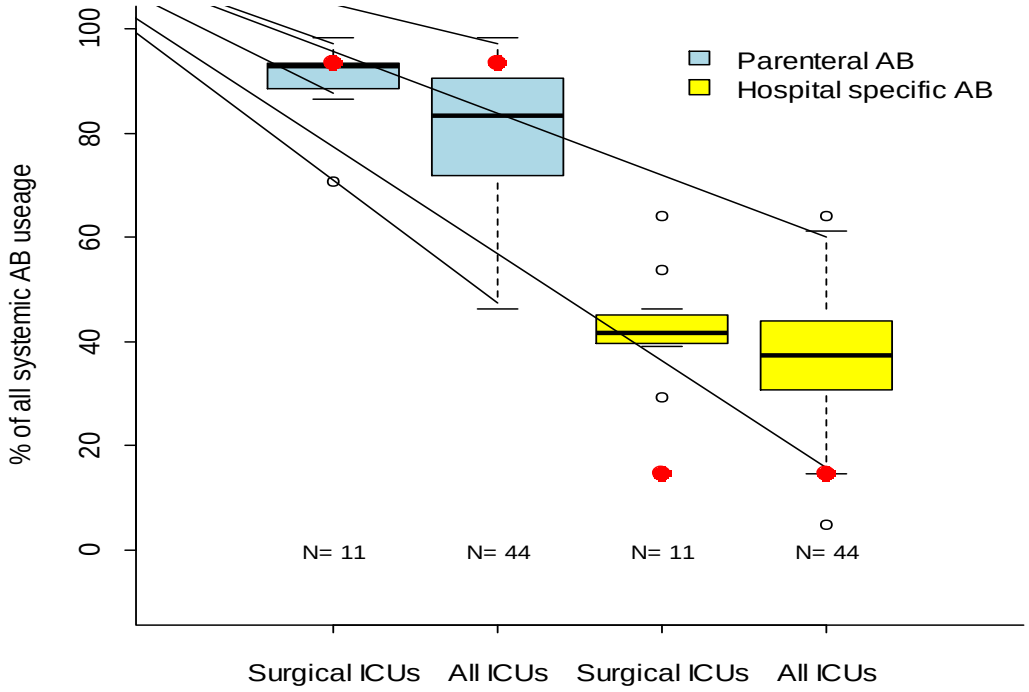
In total, 11-34 different antibacterial agents (mean: 22.0) were used in the analysed 44 units. The mean of overall antibiotic use was highest for penicillins with beta-lactamase inhibitors (19.9±8.1 DDD per 100 patient days) , followed by quinolones (17.0 ±9.3 DDD per 100 patient days) and third generation cephalosporins (15.2±9.4 DDD per 100 patient days). Similar ranking were detected in interdisciplinary and surgical ICUs. In medical ICUs the consumption of quinolones out-ranged other classes of antibacterials. Considering all ICUs in the DU90% segment five to 15 antibacterial agents were found (mean: 11.6) and the mean did not differ by ICU type (surgical: 11.7; interdisciplinary: 11.8; medical: 10.8). The proportional use of parenteral agents at Hungarian ICUs ranged from 46.2 to 98.3 % of total antibacterial use (average: 81.0%, median: 83.5%). The most frequently used oral antibiotics were the co-amoxiclav, ciprofloxacin and the moxifloxacin (Table 6).

Table 6.: Oral use of antibacterials on the surveyed Hungarian ICUs

Antibacterial agent	Parenteral use (as % of all use)	Oral use (as % of all use)	% of ALL ORAL antibiotic use
Amoxicillin and enzyme inhibitor	66.55	33.45	25.68
Ciprofloxacin	48.06	51.94	20.78
Moxifloxacin	49.33	50.67	12.74
Levofloxacin	65.72	34.28	8.74
Clarithromycin	36.81	63.19	6.28
Sulfamethoxazole and trimethoprim	7.10	92.90	5.87
Doxycycline	0.00	100.00	4.35
Clindamycin	74.76	25.24	3.55
Cefuroxime	82.91	0.00	3.50
Azithromycin	26.20	73.80	2.58
Ofloxacin	11.93	88.07	2.24
Sultamicillin	0.00	100.00	1.09
Norfloxacin	0.00	100.00	0.57
Nitrofurantoin	0.00	100.00	0.41
Amoxicillin	0.00	100.00	0.25
Roxithromycin	0.00	100.00	0.24
Ampicillin	97.88	2.12	0.23
Cefixime	0.00	100.00	0.20
Fosfomycin	0.00	100.00	0.18
Penamecillin	0.00	100.00	0.17
Ceftibuten	0.00	100.00	0.12
Pefloxacin	78.49	21.51	0.12
Cefaclor	0.00	100.00	0.09
Cefalexin	0.00	100.00	0.03

The proportional use of hospital specific and parenteral antibiotics was also slightly higher in surgical ICUs compared to all ICUs.

Figure 8: The proportional use of parenteral and hospital specific antibacterials on the surveyed ICUs. Red dots indicate the position of our ICU.



As our ICU was a nearly exclusively surgical ICU at that time I have compared our data with the data from all ICUs and then with data from the eleven surgical ICUs.

On the eleven surgical ICUs the systemic antibacterial use was between 79.77 DDD per 100 patient days and 160.54 DDD per 100 patient days. The range of the proportional use of parenteral antimicrobial use was between 70.63 % and 97.36 % in surgical ICUs.

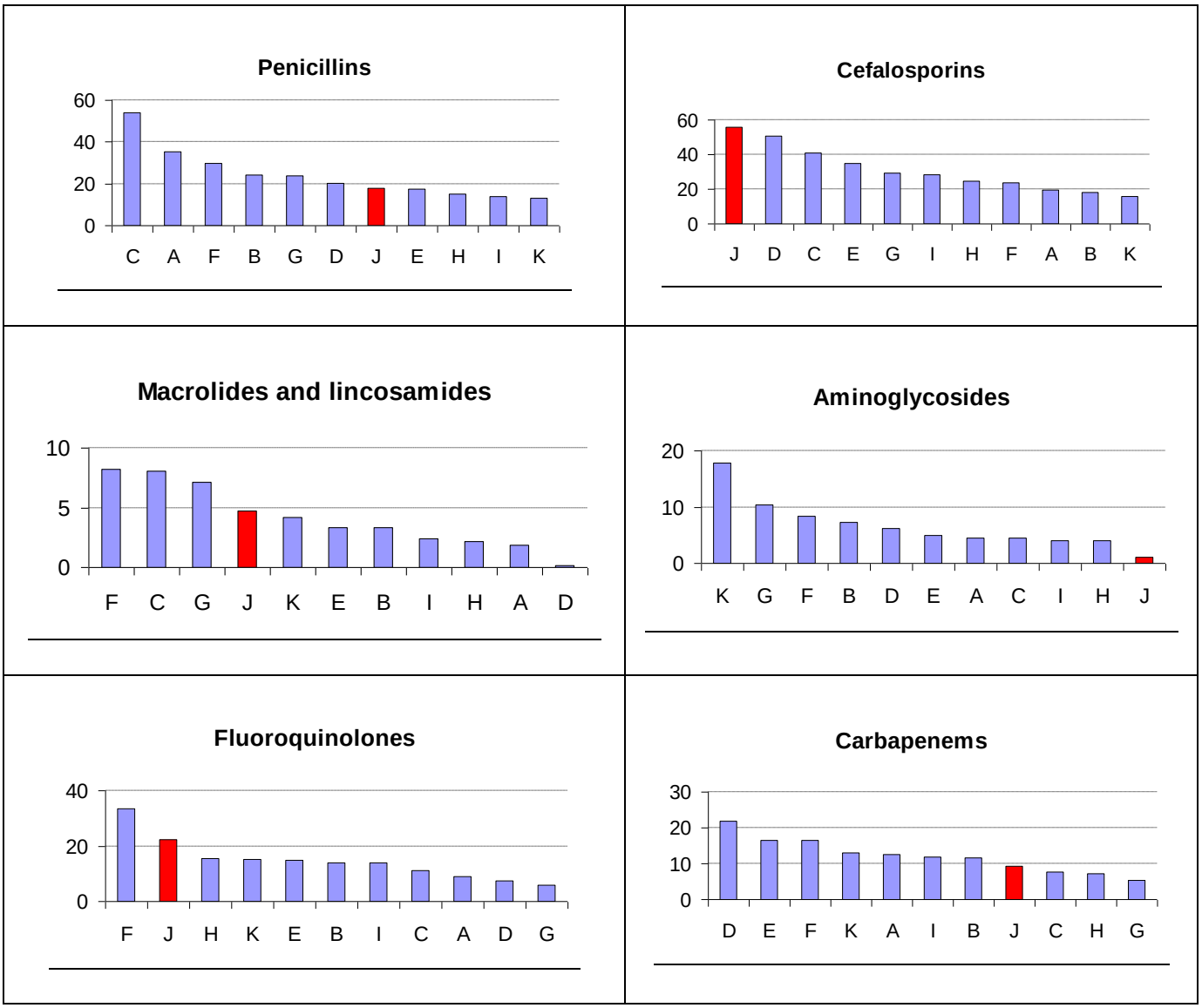
The surgical ICUs used 18 – 26 different antimicrobials (median: 24). The range of number of different antimicrobials responsible for 90% of the antibiotic consumption (DU90%) was between 8 and 14 (median: 13) (Table 8).

Table 8: Antimicrobial consumption data of the surveyed surgical ICUs. Hospital "J" represents our ICU.

Hospital	Systemic antibacterial use (DDD per 100 patient-days)	Parenteral antibiotic use (DDD per 100 patient-days)	Hospital specific antibiotic use (DDD per 100 patient-days)	Parenteral AB use (% of total AB use)	Hospital specific AB use (% of total AB use)	Number of different drug used	Number of different drug used in DU 90 %
A	88,84	83,12	26,14	93,56	29,42	23	12
B	98,83	89,84	39,8	90,9	40,27	24	13
C	139,67	129,58	58,26	92,78	41,71	26	13
D	114,43	111,4	44,59	97,36	38,97	19	9
E	125,62	108,71	54,33	86,54	43,25	18	10
F	132,42	93,53	53,25	70,63	40,21	26	14
G	100,78	93,89	44,05	93,16	43,71	24	13
H	79,77	69,45	36,89	87,06	46,25	24	14
I	160,54	157,82	86,08	98,3	53,62	21	8
J	122,62	114,61	18,02	93,47	14,7	24	10
K	114,29	103,26	73,27	90,35	64,11	26	13

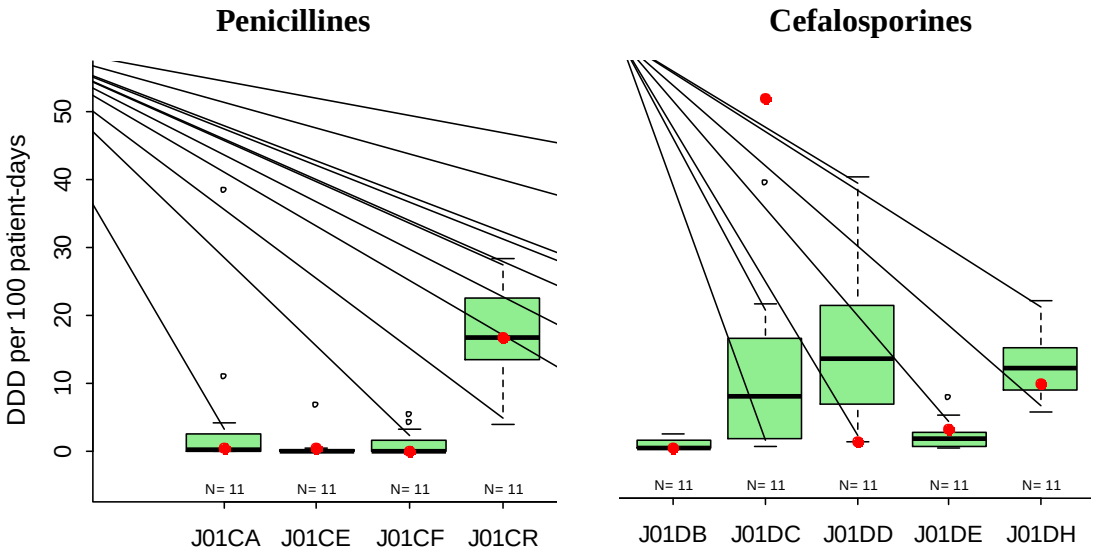
The total consumption of different antimicrobials on the surveyed surgical ICU can be seen in Figure 9.

Figure 9: The total consumption (in DDD per 100 patient days) of different antimicrobials on the surveyed surgical ICUs. Column "J" indicates our ICU.



When assessing the use of different beta-lactam antibiotics the outstanding second-generation cephalosporin (J01DC) consumption on our ICU is easily visible in Figure 10.

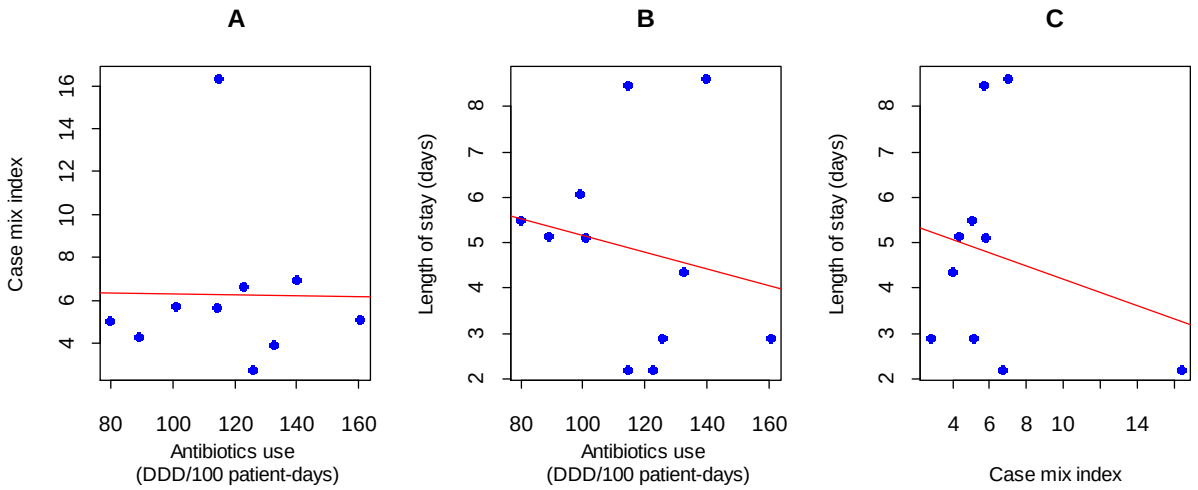
Figure 10: Use of different beta lactam antibiotics on the surveyed surgical ICUs. Red dots indicate the position of our ICU.



J01CA: Penicillins with extended spectrum; J01CE: Beta-lactamase sensitive penicillins; J01CF: Beta-lactamase resistant penicillins; J01CR: Combinations of penicillins, incl. beta-lactamase inhibitors; J01DB: First-generation cephalosporins; J01DC: Second-generation cephalosporins; J01DD: Third-generation cephalosporins; J01DE :Fourth-generation cephalosporins; J01DH: Carbapenems

On the surveyed surgical ICUs the correlation between the antimicrobial use and the LOS and the CMI was investigated and no correlation was found in any of these variables (Figure 11).

Figure 11: Correlation analysis between the antimicrobial use and the LOS and the CMI on the surveyed surgical ICUs.



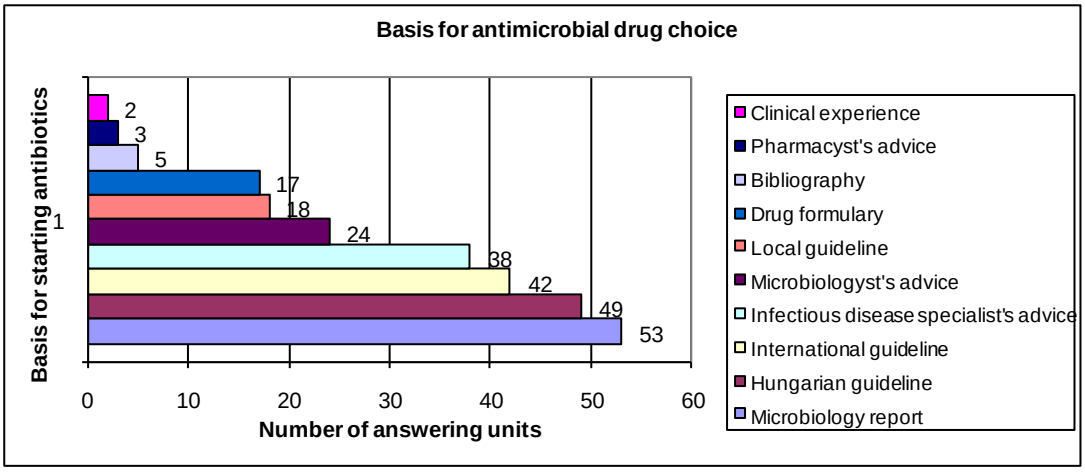
DHBD: DDD per 100 bed (patient) days, LOS: length of stay, CMI: case mix index

Surveillance on the microbiology laboratory service availability for the surveyed ICUs in Hungary

The questionairre was returned from 60 hospitals representing 62% of the targeted institutions. In 33 hospitals (55%) on-site microbiology laboratory services helped the clinicians. From the remaining hospitals the samples had to be sent away for microbiological processing and assessment.

For the intensive care physicians the microbiology report – sensitivity data – was the most important basis in deciding antimicrobial agent for a given infection. This was followed by Hungarian and international guidelines then the advice of an infectious disease specialist or a microbiologist as seen in Figure 12.

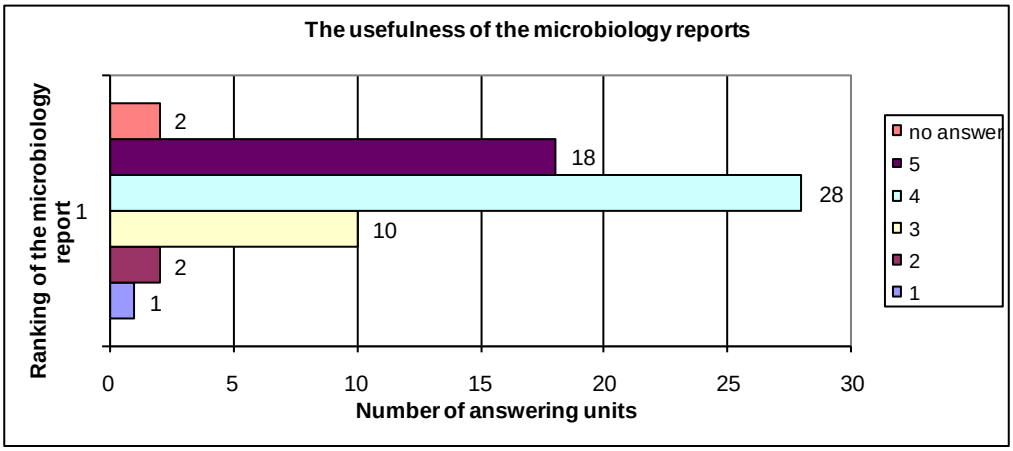
Figure 12: The basis for antimicrobial drug choice according to the importance



The turnaround time of a microbiology sample depends on the nature of the sample and the requested investigation. In our study the turnaround time of the lower respiratory tract sample used as the indicator. Ideally the negative – no growth – report of a given lower respiratory sample is available on the next day and for positive results the detailed sensitivity report is received in 48 or 72 hours after the first inoculation. According to our survey only around 50% of the positive result's sensitivity report was received during the weekdays in this ideal timeframe and less than 20% during weekends. 21 units received results electronically, 14 by post and 23 by courier and two units did not answer the question.

The satisfaction with the microbiology reports as a helping hand in starting antimicrobial therapy was asked to be ranked from 1 (worst) to 5 (best) and the average score was 4.02. The results are shown in Figure 13.

Figure 13: Satisfaction with the microbiology reports



More than half of the responding units had seen at least one confusing microbiology report where infectious disease specialist or microbiologist input would have been required. The hospitals and the ICUs were asked about the availability of the infectious disease specialist and microbiologyst consultation. At hospital level there was infectious specialist cover available for consultation in 90% of the units during working days and in 70% during out-of-hours period. Microbiologist was available for consultation in 50% of the hospitals mainly via telephone. Howewer, even this level of good cover was not used properly by ICUs as only 55% of the units reported of having asked for infectious disease consultation and 28% for microbiology consultation. Personal bedside consultation on the ICUs was even less frequent: infectious disease specialist participated in ward rounds on 11 units and microbiologist on three units with variable frequency as seen in Table 7.

Microbiology laboratories provided detailed local antimicrobial resistance data for 26 ICUs (43%).

Table 7: Frequency of bedside consultation on the surveyed ICUs by infectious disease (ID) specialist or clinical microbiologist

Frequency of bedside consultation	**ID specialist**	***Clinical microbiologist***
Daily	8	2
Every second day	1	1
Once per week	2	2
Never	48	56
No answer	1	1
Total	60	60

When assessing the microbiology laboratory services availability for the surveyed surgical ICUs (n = 11) we had the following results: (Table 8)

Table 8: Availability and different aspects of microbiology laboratory and infectious disease specialist services for the surveyed adult surgical ICUs in Hungary. Column "J" represents our ICU.

ICU	A	B	C	D	E	F	G	H	I	J	K
On site MBL	no	yes	yes	no	yes	no	no	no	yes	yes	yes
Distance from ICU (Km)	2	0	0	0.5	0	5	135	5-50	0	0	0
24 hours service	no	yes	no	yes	no	yes	no	no	yes	yes	yes
LRS TAT in weekdays (days)	3	2	2	2	2	3	3	3	3	2	2
LRS TAT in weekends (days)	3	3	3	2	4	4	4	4	2	2	4
Result sent back to ICU by	post	courier	courier	IDS	courier + IN	post + IN	post	post	IN	IN	courier + IN
Local resistance report to ICU	no	yes	no	no	no	on request	yes	yes	no	no	yes
IDS consultation in weekdays	T + P	T	T + P	T + P	P	P	P	T + P	no data	T + P	T
IDS consultation in weekends	T + P	no	T	T + P	T	T	P	T + P	T + P	T	T
MB consultation in weekdays	T	T	T	T + P	P	T	T	T + P	T + P	T + P	T + P
MB consultation in weekends	no	T	T	T	T	T	T	no	T	T	T
Attending IDS in ICU wardrounds	no	no	no	every 2nd day	no	no	no	no	no	no	no
Attending MB in ICU wardrounds	no	no	no	every 2nd day	no	no	no	no	no	no	no
Seeking IDS advice	weekly	occasionally	monthly	more than once / day	weekly	daily	daily	weekly	daily	daily	daily
Seeking MB advice	never	weekly	weekly	monthly	monthly	monthly	monthly	never	daily	daily	daily
Usefulness of the report (1: worst, 5:best)	5	5	5	5	4	5	4	3	5	5	5
Confusing MBL report	no	no	yes	no	no	yes	no	yes	no	no	yes

MBL: microbiology laboratory, LRS: lower respiratory tract sample, IDS: Infectious disease specialist, MB: microbiologist, T: telephone, P: personal, IN: intranet

Six surgical ICU had on-site microbiology laboratory background service. From the remaining five ICUs the samples had to be sent away 0.5 – 135 km for processing. The

turnaround times of the lower respiratory samples were acceptable – 2 days - on weekdays in five out of six ICUs where on-site microbiology laboratory background existed. The ICUs without such on-site laboratory background services received reports one day later in average. The off-duty (weekend) service was even slower to produce microbiology results for the ICUs, namely these were 3 - 3 – 4 – 2 – 2 – 4 days for onsite and 3 – 2 – 4 – 4 – 4 days for off-site surgical ICU units. Electronic reporting was only available only for five surgical ICUs.

To help the empirical antimicrobial therapy four ICUs received local resistance data from the microbiology laboratory services at least once in a year. One ICU had this opportunity on request.

Infectious disease specialist consultation was available for all but one surgical ICU every day. Microbiologist consultation was available for all ICUs during the week but two ICU was without microbiologist cover during the weekends. Only one ICU had attending infectious disease specialist and microbiologist during the ICU wardrounds.

Five ICUs asked advice daily from the infectious disease specialist service, three weekly, one monthly and one occasionally.

Two units never asked for an advice from a microbiologist, three asked advice daily, two weekly and four monthly.

Eight ICU was maximally satisfied with the quality of the microbiology reports.

Seven ICUs had seen at least once misleading/confusing microbiology report.

6. DISCUSSION

6.1. Local antibiotic management program

The 2001 review by Kollef summarized strategies aimed at improving antibiotic use on ICUs and enabled us to address deficiences of antibiotic prescribing system at our Institute. [6] These were mainly thought to be the lack of ID specialist in the decision making process and no limitations in antibiotic prescribing practise. In parallel a continuous increase of antibiotic use was detected. The formulation and implementation of a new local antibiotic management policy was followed by a substantial and sustained decrease in antibiotic use without corresponding increase in morbidity and mortality. There was no new dominant pathogen of bloodstream infections during this time, and the incidence of pathogens with emerging resistance mechanisms did not change substantially. This can be seen as a success as there is a worldwide tendency to the challenge posed by the growing numbers of infectious complications and multiresistant microorganisms in the hospital and ICU setting. [6, 42, 43] To our knowledge our

work was the first publication from Hungary in relation to antibiotic management program. The reduction in antibiotic use was achieved while patient characteristics data did not alter substantially. The similar number of microbiologically documented bloodstream infections in the two periods might also confirm to the absence of major bias: the policy aimed at improving antibiotic prescribing, not to modify, potentially decrease the incidence of bloodstream infections.

In this work - as with the results of the SENTRY program - *Staphylococcus aureus* was found as the predominant pathogen of bloodstream infections. [43] Distinct differences were noted in the incidence of strains with special resistance mechanisms: resistant isolates – except MRSA and oxacillin-resistant coagulase negative staphylococci – in both study periods were less frequent compared to data from SENTRY. [43] As SENTRY data was derived not only from ICU patients, the observed rare occurence of bloodstream infection pathogens with special resistances (e.g. lack of vancomycin resistant enterococci) on our ICU requires special attention. [43] Several strategies for controlling antibiotic prescribing have been previously described. [22] Similar reduction in the total antibiotic use was achieved within a French ICU with educational, restrictive and review measures. [44] A 33% reduction of antibiotic use was reported by a German surgical ICU by implementation of a revised guideline. [45] Our local antibiotic management program involved a restrictive strategy with the following two elements: limited prescribing authority and compulsary consultation with the nominated ID specialist. The ID specialist consultation had educational effect as well.

The restrictions were applied for all antibacterials for therapeutic use and resulted in decreased use of almost all antibiotic classes rather than a decreased use of restricted antibiotics with a compensatory increase in the use of non-restricted ones – known as the ‘‘squeezing-the-balloon’’ effect. [46]

The average level of antibiotic use, achieved after the policy implementation (2003–2005) was in middle range when compared to surgical ICUs from other European countries. [45, 47–50] However, as factors that are already proven to correlate with antibiotic use [48, 50] (e.g. length of ICU stay, hospital affiliation and size) or possibly could influence antibiotic use (e.g. patient case-mix, type of surgical patients) have not always been revealed in published studies [45, 47–50], any differences in antibiotic use must be cautiously interpreted. It must be emphasized that the majority of our case mix were postoperative patients with short term ICU stay and consequently had often received prophylaxis with cefuroxime. The increasing number of admissions might only partly explain the further escalation of cefuroxime use.

The reduction in antibiotic usage was not associated with either a change in microbiological outcome (number of bloodstream infections, number of pathogens with special

resistance mechanisms), or mortality. Generally, as discussed by MacDougall [22], other studies have also found no difference or a slight improvement in clinical outcomes with antimicrobial management programs. There is growing evidence that the multidisciplinary team approach, with the leading role of an ID specialist, is crucial for the sucess of an antimicrobial stewardship program. [22, 51, 52] However, this approach is seldom used in Eastern or Central Europe as reflected by the scarcity of the literature. Significant barriers to the involvement of an ID specialist also exist in other parts of the world. [22] The personal day by day presence of the nominated ID specialist has several advantages including educational opportunities [22] which could be detected in changes in practise (e.g. the suspected colonized lines are now removed immediately without starting vancomycine as was routine previously). In summary, this work supports the view that setting up a local antibiotic management program with restricted prescribing authority and involvement of an ID specialist in clinical decision-making is an effective tool for the control of the antibiotic use in the ICU setting. This work also helped in highlighting other fields of possibly inappropriate antibiotic use and therefore appointed future aims.

However, the limitations of the study must be acknowledged. This was a single-centered study where only quantitative but not qualitative data on antibiotic use was collated. The lack of patient-level antibiotic use data also limited our ability to analyse antibiotic use in depth.

Other possible confounding factors (e.g. other than bloodstream infections, nursing habits) were not explored. Finally, it cannot be ignored that ICU patient turnover increased during the course of the analysis.

6.2. Revised surgical antimicrobial prophylaxis program

As the profile of our intensive care unit did not change and no other alterations were made on the previously proven ongoing local antibiotic management program [53] we conclude that the modification of the surgical antimicrobial prophylaxis alone was responsible for the significant reduction in total antibiotic use. Prior to this intervention the antibiotics were given to patients for days, sometimes during their entire stay on ICU. We are aware that the single shot surgical antibiotic prophylaxis is already proven to be effective but this programme seemed to be the only possible compromise at that time. [54] The new management system was brought in 2006 therefore we consider this year as a transition year. In 2006 the cefuroxime consumption platoed as taking over the responsibilities from the surgeons were brought in and to apply the automatic stop order was not without difficulties. After 2006 the cefuroxime consumption showed a steady and steep decline. The clindamycine use increased during the second period but the vancomycine use decreased paralelly. We explain this phenomenon with the more careful

selection of the prophylaxis in case of cephalosporine (beta – lactam) hypersensitivity. After the introduction of the new policy vancomycine was only used if it was really indicated. When assessing the impact of this work one has to be aware that antibiotic use on our ICU before the implementation of the new management programme was already similar to German surgical ICUs (mean antibiotic use 1104 DDD per 1000 patient days) [48]. With this programme a further 15% decrease in the antibiotic usage was gained and we believe that we have reached the near optimal antibiotic consumption range for our ICU. These achievements are comparable to a similar successful programme published by Meyer et al. where – contrary to our work – they have concentrated only on a special patient group with external cerebrospinal fluid drainage. [55] It is important to show that the decrease of the second generation cephalosporins and other agents used for the prophylaxis did not come with the compensatory increase of other antibiotics (squeezing the balloon effect). [46]

There are limitations of our results: firstly due to the postoperative nature of our ICU the mean LOS was 2.2 days, therefore the possible negative effect of the new surgical prophylaxis programme - e.g. increasing number of surgical site infections – would have arisen in wards where the patients were transferred. As neither during, no since the study period has any claim been received regarding this issue from the other wards, we do not believe that such a negative impact was observed. As our ICU was responsible for the management of the critically ill post-surgical patients, any trend of transferring critically ill ex-ICU patients emerging would have been obvious from the case-mix reports. For the same reason – short LOS and high patient turnover rate – the microbial resistance was beyond the scope of this work.

Secondly we did not investigate the impact of this programme on the cost of care. In Hungary during the last decade we have witnessed so many economical and regulatory changes that the inclusion of the cost analysis to this work was impossible.

Last but not at least this work was based on aggregated antibiotic consumption data therefore the power of the patient level data analysis is missing.

In conclusion our work supports that targeting antibiotic prophylaxis on surgical ICU - and possible in non intensive care surgical wards – can be a promising aim reducing inappropriate antibiotic usage.

6.3. National survey on antimicrobial consumption and on the availability of microbiology laboratory services on adult intensive care units in Hungary

Antibiotic consumption on the intensive care units varied from 27.91 to 167.79 DDD per 100 patient-days and from 79.77 to 160.54 DDD per 100 patient-days on surgical ICUs.

The median and mean consumption was 98.38 DDD per 100 patient-days and 102.11 DDD per 100 patient-days on Hungarian ICUs and these numbers are lower than antimicrobial consumption data from from other European countries. [41, 56, 57]

The several fold difference in the total antibiotic use on ICUs is not unique in Europe as it was published in a German and in other European study. [41, 56, 57]

In a Swedish study researchers found that antibiotic consumption was higher on tertiary ICUs. [58] Our ICU is a tertiary ICU and as a tertiary ICU our CMI was higher than average so as expected the antimicrobial consumption was high if compared to all and to the surgical ICUs.

The LOS on our ICU was amongst the lowest compared to surgical or all ICUs. Since the LOS in general is related to the formula used to express antimicrobial use in DDD per 100 patient-days its influence on antimicrobial use has already been investigated in different studies: some claimed that shorter LOS may result in higher antibiotic use when expressed as DDD per 100 patient-days [59, 60] and other found positive correlation between antimicrobial consumption and average LOS on ICUs. [18] In our study, antibiotic use on the studied Hungarian surgical ICUs was not in correlation with the LOS.

One could expect higher antibiotic use on surgical ICUs where the CMI is higher. In our work we could not find such a connection between these parameters. In another study the authors could not find association between an illness severity score and the level of antibiotic use. [61] Such a relationship could have been concealed because both the case mix index and other patient severity scores correlate with the average condition of the patients not with the severity of their infections.

Hospital-specific antibiotics are defined by the European Surveillance of Antibiotic Consumption (ESAC) project, as carbapenems, glycopeptides, aminoglycosides and third- and fourth-generation cephalosporins, monobactams. [62] The hospital specific antimicrobial consumption (both in absolute and relative manner) was one of the lowest on our ICU and we do consider it as the fruit of our antibiotic stewardship efforts. This is in line with a Swedish study where low antibiotic use on ICUs was considered as the result of their strong control efforts. [47]

In our study the range of the proportional use of oral agents was between 1.70 and 53.85 % of total antimicrobial use. The high oral antimicrobial consumption on some ICUs may be alarming because of bioavailability issues in critically ill patients or it could be explained by the inappropriate patient discharge/admission policy. [63-65] On our ICU oral antibiotics contributed to less than 10% of all antimicrobial consumption. Due to missing data in the international literature it is difficult to compare these results to other works but in a study from Sweden the authors reported up to 13% and 26% oral antimicrobial use on a surgical and

medical ICU, respectively. [47] Association between all antibiotic use and the proportional use of oral antibiotics could be assumed – more antibiotic use might comes together with more oral consumption – but in this present work the higher proportional use of oral agents was not associated with the magnitude of antibiotic use (data not shown).

In our study the most commonly used antimicrobials on the studied ICUs (and also when considering only surgical ICUs) were penicillins with beta-lactamase inhibitors, quinolones and third-generation cephalosporins, same as in a recent German study. [66] On our ICU - contrary to other surgical ICUs - second generation cephalosporins (mainly cefuroxime) were the most frequently used antibiotics. This outstanding second generation cephalosporin consumption was significantly reduced as the result of the altered surgical antibiotic prophylaxis policy.

The cefuroxime was the most frequently used class of antibiotics in a recent Swedish study as well. [67]

Tha antibiotic use pattern was very different on the surveyed surgical ICUs but there were very specialised units amongst them (e.g. Országos Szívsebészeti Intézet). This makes the quality assessment and any comparison between the units very difficult.

A considerable variation in the number of used antibacterials and in the number of antibacterials in the DU90% segment was found in our study. As other ICU studies from adult units have not published these kinds of data, we could not make a comparison. However a recent study from neonatal ICUs in the Netherlands showed similar variations in the number of used agents (nine to 24) and in the number of agents (three to ten) used in the DU90% segment. [68] The reported lower number of used antibacterials in the Dutch study is reasonable, as the number of recommended antibacterial agents in neonates is lower.

The basis for an effective and aimed antimicrobial therapy is the accurate and quick microbiology report. It is even more important on ICUs where immunocompromised patients are treated and multiresistant microorganisms are common. Our survey showed that the microbiology report was the most important basis in deciding the antimicrobial therapy on the majority of the ICUs. Infectious disease specialist’s advice and advice from a microbiologist were important as well. Even though other results of our survey showed a disappointing picture: on the majority of the ICUs the microbiology laboratory background was partially or completely missing therefore targeted antimicrobial therapy was simply not possible. With this missing laboratory background the late start - or late de-escalation - of a sensitivity report guided antimicrobial therapy is inevitable.

In this work the turnaround time of the lower respiratory tract samples was one of the indicator to assess the availability (and in some extent the quality) of the microbiology laboratory services. As discussed above ideally the physician should be able to see the detailed sensitivity report in positive cases within 48-72 hours. The results of the survey showed much slower than ideal turnaround time during weekdays and unacceptable quality services during weekends.

The detailed sensitivity report for a given ICU helps to keep the focus on the ever changing resistance data therefore it serves as the foundation for a local antimicrobial guideline. This was one of the conclusions of the Antibiotic Stewardship project run in 2005 – 2006. [69] As another important message from the same project they suggested to use the local resistance data when adapting international antimicrobial therapeutic guidelines to obtain the most effective results. According to our survey only 38% of the Hungarian adult ICUs received such a report resulting in one of the important basis for local antimicrobial guidelines is missing.

The institutional existence of the microbiological laboratory services is an important issue too. It is very difficult to provide up-to-date reports if the samples should travel long distances to reach the microbiology laboratory, or if there is no out-of-hours microbiologist or infectious disease specialist cover. The clinical laboratory background for ICUs is compulsory but the microbiology laboratory background is not. [70]

Every ICU reported in our survey that the physicians had at least one confusing microbiology report. As the accuracy of the report is very paramount to start the appropriate antimicrobial therapy the discussion with an infectious disease specialist or a clinical microbiologist to clarify the report is vital. During this clinical discussion the circumstances of the sampling, the condition of the patient and other professional issues are discussed and at the end an agreed antimicrobial strategy is made. Unfortunately it become clear that ICUs are not using the opportunities for such consultations even in hospitals where microbiology and infectious disease specialist background is present.

The first part of this PhD thesis proves that infectious disease specialist and microbiologist consultation helps to keep antibiotic usage, resistance - and potentially cost - in bay. Still, ICUs in Hungary do not use this tool to improve their infection control strategies.

Even worst the gaps in the availability of the microbiology services might undermine the efforts made to achieve better treatment and survival of sepsis in Hungary.

7. SUMMARY

In this thesis I set out to provide the results of an ongoing local antibiotic stewardship program from 2000 to 2009. I also intended to provide the results of a national survey on antimicrobial consumption and on the availability of microbiology laboratory services on adult intensive care units in Hungary.

My main findings are as follows:

- The first part of this work showed that the estimated mean antibiotic consumption decreased significantly to 101.3 DDD per 100 patient-days from 162.9 DDD per 100 patient-days after the introduction of the local antibiotic management program. The mortality and the number of bloodstream infections did not change significantly in the two periods. This work supports the view that a well performed local antibiotic management program with restricted prescribing authority and involvement of an infectious disease specialist in clinical decision-making is an effective tool for controlling the antibiotic use on ICU setting.

- Subsequently, segmented regression analysis revealed that the estimated mean antibiotic consumption showed further significant decrease from 101.3 DDD per 100 patient-days to 86.0 DDD per 100 patient-days after the introduction of the new antimicrobial prophylaxis policy. With this programme a further 15% decrease in the antibiotic usage was achieved and I believe that we have reached the near optimal antibiotic consumption range for our ICU. Very simple intervention resulted in the changes and our program can be introduced relatively easily on other ICUs. It is important to see that the decrease of the second generation cephalosporins and other agents used for the prophylaxis did not come with the compensatory increase of other antibiotics.

- The national survey on antimicrobial consumption on adult intensive care units in Hungary showed that the consumption of systemic antibacterials was between 27.9 and 167.8 DDD per 100 patient-days. We could not find association between the antibiotic consumption and the CMI or the LOS. The proportional use of parenteral agents on Hungarian ICUs ranged from 46.2 to 98.3 % of total

antibacterial use. A considerable variation in the number of used antibacterials and in the number of antibacterials in the DU90% segment was also found in our study. It was not possible to explain these differences in details as for many Hungarian ICUs this was the first ever occasion when antimicrobial use was expressed in a standardized consumption unit. Still this work enabled us to identify extreme values on different ICUs (e.g. high proportion of oral antibiotics, low number of antibiotics in the DU90 range) wich would require further analysis and/or intervention. The severalfold differences in antimicrobial consumption may indicate a need for a structured, more frequent and more detailed data collection and analysis.

- The survey on availability of microbiology laboratory services on adult intensive care units in Hungary showed a disappointing picture: on the majority of the ICUs the microbiology laboratory background was partially or completely missing therefore targeted antimicrobial therapy was simply not possible. The analysis of the turnaround time of the lower respiratory tract samples were much slower than ideal during weekdays and unacceptable during weekends mainly due to missing microbiology laboratory background. Even where microbiology laboratory was available the ICU physicians frequently did not use the opportunity for infectious disease specialist/microbiologist consultation.

In conclusion, the continuous effort to control and to monitor the use of antimicrobial agents at local and national level is an important tool to keep inappropriate antibacterial use at bay and to highlight problems which may require interventions.

The institutional problem with missing microbiology laboratory services undermine the efforts to provide quick and accurate reports therefore decrease the chance of the survival of a critically ill patient with life threatening infection.

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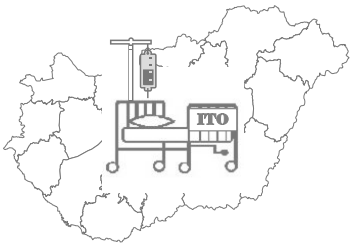
10. APPENDIX



Kérdőív a hazai intenzív osztályok **2006** évi antibiotikum alkalmazási szokásairól, rendjéről és mikrobiológiai laborhátteréről

Prof. Dr. Bogár Lajos által elektronikusan küldött változat nyomtatott verziója

Kórházi bizottságok

1. Volt-e az Önök kórházában **2006**-ban gyógyszerterápiás bizottság?

   ❑ Igen ❑ Nem ha **NEM** a válasza, kérjük **folytassa a 4. kérdéssel**

2. Ha igen, kik voltak a tagjai a gyógyszerterápiás bizottságnak?

   ❑ Belgyógyász ❑ Laborvezető ❑ Gazdasági igazgató
   ❑ Klinikai mikrobiológus ❑ Infektológus ❑ Főgyógyszerész
   ❑ Sebész szakorvos ❑ Neurológus ❑ Intenzív terápiás
   ❑ Kórházhigiénikus szakma :_____ ❑ Gyermekgyógyász ❑ Egyéb

3. Milyen gyakran ült össze a gyógyszerterápiás bizottság?

   ❑ Negyedévente ❑ Félévente ❑ Évente ❑ Ritkábban, mint évente

4. Volt az Önök kórházában **2006**-ban **külön** antibiotikum bizottság ?

   ❑ Igen ❑ Nem ha **NEM** a válasza, kérjük **folytassa a 7. kérdéssel**

5. Ha igen, kik voltak a tagjai az antibiotikum bizottságnak ?

   ❑ Orvosi mikrobiológus ❑ Infektológus ❑ Gyógyszerész
   ❑ Intenzív terápiás szakorvos ❑ Kórházhigiénikus ❑ Gyermekgyógyász
   ❑ Belgyógyász ❑ Laborvezető ❑ Sebész
   ❑ Egyéb szakma :_____

6. Milyen gyakran ült össze az antibiotikum bizottság ?

   ❑ Negyedévente ❑ Félévente ❑ Évente ❑ Ritkábban, mint évente

7. Stratégiai célja volt **2006**-ban a kórházvezetésnek az antibiotikum alkalmazás javítása/fejlesztése?

   ❑ Igen ❑ Nem

Antibiotikum Politika

8. Volt-e **2006**-ban az Önök kórházában gyógyszer alaplista, melyben feltüntették a kórházban elérhető gyógyszerek, antibiotikumok körét ?

   ❑ Igen ❑ Nem

A következő kérdések az intenzív terápiás osztályra vonatkoznak:

9. Kik voltak jogosultak **2006**-ban az intenzív osztályon fekvő beteg részére antibiotikum terápiát **indítani** ?

   ❑ Osztályos orvos ❑ Osztályos szakorvos ❑ Rezidens orvos
   ❑ Osztályvezető orvos ❑ Egyéb orvos:_____

10. Más osztályról, műtőből átvett beteg esetén volt-e jogosultsága **nem** az Önök intenzív osztályán dolgozó orvosnak antibiotikum terápiát **indítani, leállítani, vagy megváltoztatni**?

❑ Igen ❑ Nem

11. 2006-ban volt olyan antibiotikum melynek felírása/használata engedélyhez kötött volt az Önök intenzív osztályán ?

❑ Igen ❑ Nem ha **NEM** a válasza, kérjük **folytassa a 15. kérdéssel**

12. Ha igen, mely formákra vonatkozott az engedélyeztetés ?

❑ Orális ❑ Intravénás

13. Ha igen, mely antibiotikumcsoportokra vonatkozott az engedélyeztetés ?

❑ Fluorokinolonok (pl. Ciprobay, Avelox, Tavanic)
❑ Glikopeptidek (pl. Vancomycin, Targocid)
❑ Széles spektrumú penicillinek (pl. Standacillin)
❑ Béta-laktamáz gátlóval kombinált *széles spektrumú* penicillinek (pl. Augmentin, Tazocin)
❑ Harmadik generációs cefalosporinok (pl. : Claforan, Fortum, Rocephin, Megion, stb)
❑ Negyedik generációs cefalosporinok (Maxipime)
❑ Karbapenemek (pl. Tienam, Meronem)
❑ Makrolidok (pl. Klacid, Sumamed, Zitrocin)
❑ Lincosamidok (pl. Dalacin C)
❑ Aminoglikozidok (pl. Amikin, Netromycine)
❑ Egyéb :_____

14. Ki volt jogosult ezen antibiotikumok használatának **végső engedélyezésére** ?

❑ Osztályvezető főorvos ❑ Osztályos Szakorvos ❑ Infektológus
❑ Intézetvezető professzor/főigazgató ❑ Gyógyszerész ❑ Egyéb:_____

15. Volt-e **2006-ban helyi**, az antibiotikumok **terápiás** használatára vonatkozó **írott** irányelv (=antibiotikum politika) az Önök intenzív terápiás osztályán ?

❑ Igen ❑ Nem ha **NEM** a válasza, kérjük **folytassa a 24. kérdéssel**

16. Ha igen, kik határozták meg annak szakmai tartalmát ?

❑ Gyógyszerterápiás bizottság ❑ Antibiotikum bizottság ❑ Gyógyszerészek
❑ Mikrobiológus/infektológus konzulens ❑ Intenzív terápiás szakorvos
❑Egyéb :_____

17. **2006. dec. 31.–et** megelőzően mikor dolgozták át utóljára ezen antibiotikum politikát?_____

18. Minden intenzív osztályos orvos számára **könnyen hozzáférhető** volt az antibiotikum politikára vonatkozó kiadvány ?

❑ Igen ❑ Nem

19. Megítélése szerint Ön illetve munkatársai mennyire gyakran használták az antibiotikum politikára vonatkozó kiadványt?

❑ Naponta ❑ Hetente ❑ Havonta ❑ Ritkán ❑ Soha

Empirikus terápia az intenzív osztályon

A következő kérdések az intenzív terápiás osztályra vonatkoznak :

20. A 15.-ös pontban említett kiadvány tartalmazott-e bizonyos **infekciók empírikus** antibiotikum kezelésére nézve ajánlásokat/irányelvet ?

❑ Igen ❑ Nem

21. Ha igen, mire vonatkozóan tartalmazott információt?

❑ Konkrét hatóanyagok
❑ Első választandó antibiotikum
❑ Adagolás
❑ Alkalmazás időtartama
❑ Egyes antibiotikum csoportok
❑ Alternatív választás
❑ Alkalmazás módja (pl. iv)
❑ Mellékhatás
❑ Egyes mikroorganizmusok antibiotikum kezelése

22. Az irányelv ajánlotta-e az empírikus terápia felülvizsgálatát és szükség szerint antibiotikum váltást/alternatívát?

❑ Igen ❑ Nem

23. Ha igen, hány nap antibiotikum alkalmazás után ? _____nap

24. Ön szerint milyen információforrásokat használtak az intenzív osztályon dolgozó orvosok az **antibiotikum felíráshoz való döntésnél** ?

❑ Nemzetközi ajánlás ❑ Hazai ajánlás ❑ Helyi ajánlás
❑ Mikrobiológus tanácsa ❑ Infektológus tanácsa ❑ Gyógyszerész tanácsa
❑ Gyógyszeradatbázis (pl. Gyógyszer kompendium)
❑ Ha van, mikrobiológiai lelet
❑ Bibliografikus adatbázis (Pubmed,Medline)
❑ Egyéb :_____

25. Melyek bizonyultak Ön és kollegái számára ezek közül a **három** leghasznosabbnak ?

❑ Nemzetközi ajánlás ❑ Hazai ajánlás ❑ Helyi ajánlás
❑ Mikrobiológus tanácsa ❑ Infektológus tanácsa ❑ Gyógyszerész tanácsa
❑ Gyógyszeradatbázis (pl. Gyógyszer kompendium)
❑ Ha van, mikrobiológiai lelet
❑ Bibliografikus adatbázis (Pubmed,Medline)
❑ Egyéb :_____

Kórházi antibiotikum prophylaxis politika

26. Volt-e az Önök **kórházában 2006-ban** sebészi antibiotikum prophylaxisra vonatkozó ajánlás/irányelv?

❑ Igen ❑ Nem ha **NEM** a válasza, kérjük **folytassa a 29. kérdéssel**

27. Ha igen, milyen szakmák vettek részt az irányelv kidolgozásában ?

❑ Gyógyszerterápiás bizottság ❑ Antibiotikum bizottság ❑ Infektológus
❑ Mikrobiológus ❑ Sebész ❑ Gyógyszerész
❑ Aneszteziológus/Intenzív terápiás szakorvos

28. A sebészi antibiotikum prophylaxis irányelv kitér:

❑ Azon műtétek listájára, ahol antibiotikum prophylaxist szükséges alkalmazni
❑ Az első választandó antibiotikumra
❑ Az alternatív antibiotikumra (pl. gyógyszerallergia esetén)
❑ Egyszeri dózisú prophylaxisra
❑ A prophylaxis szükséges időtartamára
❑ Az antibiotikum adás időzítésére
❑ Adott antibiotikum kórokozó spektrumára
❑ Az alkalmazandó dózisra
❑ Az alkalmazás módjára
❑ Napi terápiás költségre
❑ Ismételt adagolásra hosszú műtét vagy nagy vérveszteség esetén
❑ Mellékhatásokra

29. Az prophylaxis ideális időtartamának (<24h) túllépése esetén volt-e **rendszeresen** bármiféle figyelmeztetés valaki (aneszteziológus, gyógyszerész, infektológus) részéről a rendelő orvos felé?

❑ Igen ❑ Nem

30. A sebészi antibiotikum prophylaxis rendeléséért ki volt a felelős a **műtétet megelőzően** ?

❑ Operáló sebész ❑ Aneszteziológus/Intenzív terápiás szakorvos ❑ Egyéb:_____

31. Amennyiben a beteg az intenzív osztályra került a **műtét után**, az antibiotikum alkalmazás **további folytatását** ki rendelte el leggyakrabban?

❑ Operáló sebész ❑ Aneszteziológus/Intenzív terápiás szakorvos
❑ Infektológus ❑ Egyéb személy :_____

Oktatás

A következő kérdések az intenzív terápiás osztályra vonatkoznak :

32. A **2006**-ot megelőző **2 évben** a következők közül **szervezett formában** az intenzív osztályon dolgozó orvosok honnan nyerhettek **információt** az antibiotikumok használatával kapcsolatban?

- ❑ Nem gyógyszercég által szponzorált előadás
- ❑ Oktató/komputer program
- ❑ Osztályos referálókon esetbemutatás, irodalom áttekintés
- ❑ Konzílium
- ❑ Gyógyszercég által szponzorált gyógyszerismertető előadás
- ❑ Konferencián való résztvétel
- ❑ Egyéb :_____

❑ Önszorgalomból, autodidakta módon fejlesztették ismereteiket

33. A **2006**-ot megelőző **2 évben** az intenzíves szakszemélyzet részesült-e **belső/helyileg** szervezett oktatásban ?

Az antibiotikum használatról : ❑ Igen ❑ Nem
Az antibiotikum rezisztencia következményeiről: ❑ Igen ❑ Nem

ha **NEM** a válasza, kérjük **folytassa a 38. kérdéssel**

34. A belső/helyileg szervezett oktatás, annak oktatási anyaga konkrétan az intenzív osztályos személyzetre irányult ?

❑ Igen ❑ Nem

35. Ki szervezte a belső/helyi oktatást ?

- ❑ Mikrobiológus/infektológus/kórházhigiénikus
- ❑ Gyógyszerterápiás bizottság vagy antibiotikum bizottság
- ❑ Gyógyszerészek ❑ Gyógyszerforgalmazó cég ❑

Egyéb :_____

36. Milyen gyakorisággal tartottak ilyen belső/helyileg szervezett oktatást, továbbképzést az antibiotikummokal kapcsolatosan az intenzív osztályon?

- ❑ Folyamatosan ❑ Félévente ❑ Háromhavonta
- ❑ Évente ❑ Ritkábban,mint évente

37. Történt-e bármiféle felmérés az oktató kampányok effektivitásáról ?

❑ Igen ❑ Nem

Felmérések és auditok (individuális antibiotikumrendelések megfelelősségének értékelése)

A következő kérdések az intenzív terápiás osztályra vonatkoznak :

38. A **2006**-ot megelőző **2 évben** történt-e felmérés, kimutatás az antibiotikum használat jellemzőiről az intenzív terápiás osztályon?

❑ Igen ❑ Nem ha **NEM** a válasza, kérjük **folytassa a 42. kérdéssel**

39. Ha igen (38. kérdés) az mire irányult ?

❑ Pénzügyi vonatkozás (pl. mennyit költöttek az adott évben/hónapban antibiotikumokra)
❑ Gyakorisági jellemzők (pl. betegek hány százaléka kapott antibiotikumot)
❑ Nyers mennyiségi jellemzők (pl. dobozszámban kifejezett karbapenem fogyás 2 különböző időszakban)
❑ Standardizált mennyiségi jellemzők (pl. napi átlagos felnőtt dózisra az ún. Defined Daily Dose -DDD-re vonatkoztatott fogyás, pl. DDD/100 ápolási napban kifejezett antibiotikum fogyás)
❑ Minőségi jellemzők (pl. mennyire tartják be az irányelv egyes pontjait)

40. Ha igen (38. kérdés), ki végezte ezen felméréseket ?

❑ Gyógyszerészek ❑ Antibiotikum bizottság
❑ Intenzív orvosok ❑ Sebészek
❑ Gyógyszerterápiás vagy antibiotikum bizottság ❑ Klinikai mikrobiológus/infektológus
❑ Egyéb személy :_____

41. Az osztályon dolgozók közük **ki** és **hogy** kapott visszajelzést a felmérésről ?

❑ Nem kaptak visszajelzést
❑ A felíró orvosok személyesen, levélben
❑ Az osztályvezető főorvos, levélben
❑ Referálón prezentáció
❑ Egyéb módon :_____

Mikrobiológiai laboratórium szerepe

42. Működött-e mikrobiológiai vizsgálatot végző laboratórium vagy részleg a kórházban **2006**-ban?

❑ Igen ❑ Nem

43. Ha nem, milyen távolságra volt az elérhető mikrobiológiai laboratórium, amelynek a szolgáltatásait igénybe vették?

_____ km

A következő kérdések az intenzív terápiás osztályra vonatkoznak, **2006 évre** :

44. Biztosított-e a mikrobiológiai laboratórium hétvégi (szombat, vasárnap, ünnepnap) **eredményközlést**?

❑ Igen ❑ Nem

45. Volt-e lehetőség munkaszüneti napokon is bakteriológiai vizsgálatot küldeni úgy, hogy az feldolgozásra is került?

❑ Igen ❑ Nem

46. A vizsgálati anyagot fogadta-e a mikrobiológiai laboratórium 24 órán keresztül?

❑ Igen ❑ Nem

47. Az elküldéstől számítva hány napon belül kaptak alsó légúti minta **pozitív tenyésztési** eredményt, ha a mintát **hétfő és csütörtök** között küldték?

❑ 1 nap ❑ 2 nap ❑ 3 nap ❑ 4 nap

48. Az elküldéstől számítva hány napon belül kaptak alsó légúti minta **pozitív tenyésztési** eredményt, ha a mintát **péntek és vasárnap** között küldték?

❑ 1 nap ❑ 2 nap ❑ 3 nap ❑ 4 nap

49. Közöltek-e mikrobiológiai lelet részeredményt telefonon ?

❑ Igen ❑ Nem

50. Hogyan történt a mikrobiológiai lelet végső közlése ?

❑ Kézbesítő (pl. beteghordó) ❑ Posta ❑ Intraneten ❑ Email

❑ Egyéb :_____

51. A mikrobiológiai laboratórium közölt-e az **<u>osztályra vonatkozó összesített</u>** rezisztencia adatokat **írásban** az **empírikus** antibiotikum választás segítése céljából ?

❑ Igen ❑ Nem <u>ha **NEM** a válasza, kérjük **folytassa a 54. kérdéssel**</u>

52. Ha igen, milyen gyakran közölték az osztályra vonatkozó összesített rezisztencia adatokat **2006**-ban?

❑ Évente több, mint kétszer ❑ Évente kétszer ❑ Évente egyszer

53. Ki kapta meg az **írásbeli** információt az összesített rezisztencia adatokról ?

❑ Az osztályvezető főorvos ❑ Minden egyes orvos személyesen
❑ Intézetvezető professzor/főigazgató ❑ Egyéb személy :_____

54. Közölt-e a mikrobiológiai laboratórium MIC (minimális gátló koncentráció) értéket a laborleleten ?

❑ Igen, mindíg ❑ Igen, bizonyos esetekben
❑ Igen, de csak kérésre ❑ Nem

55. Milyen lehetőség volt **az infektológus konzílium** kérésére <u>munkaidőben</u>?

❑ Telefonos ❑ Személyes ❑ Nem volt lehetőség

56. Milyen lehetőség volt a **mikrobiológus konzílium** kérésére <u>munkaidőben</u>?

❑ Telefonos ❑ Személyes ❑ Nem volt lehetőség

57. Milyen lehetőség volt az **infektológus konzílium** kérésére <u>munkaidőn kívül</u>?

❑ Telefonos ❑ Személyes ❑ Nem volt lehetőség

58. Milyen lehetőség volt a **mikrobiológus konzílium** kérésére <u>munkaidőn kívül</u>?

❑ Telefonos ❑ Személyes ❑ Nem volt lehetőség

59. A napi viziteken rendszeresen jelen volt-e /segítette-e a terápiát mikrobiológus ?

❑ Igen ❑ Nem

60. A napi viziteken rendszeresen jelen volt-e /segítette-e a terápiát infektológus ?

❑ Igen ❑ Nem

61. Milyen gyakran kértek tanácsot a mikrobiológustól az antibiotikum alkalmazással kapcsolatban?

❑ Naponta többször ❑ Naponta ❑ Hetente ❑ Havonta ❑ Soha

62. Milyen gyakran kértek tanácsot az infektológustól az antibiotikum alkalmazással kapcsolatban ?

❑ Naponta többször ❑ Naponta ❑ Hetente ❑ Havonta ❑ Soha

63. A mikrobiológiai laboratórium végzett-e anaerob tenyésztést/azonosítást?

❑ Igen ❑ Nem

64. A mikrobiológiai laboratórium végzett-e gomba tenyésztést/pontos azonosítást?

❑ Igen ❑ Nem

65. Rendelkeztek-e bakteriológiai mintavételi protokollal?

❑ Igen ❑ Nem

66. Ön szerint (1-5 ig skálán, 1=abszolút nem ; 5= kifejezetten) mennyire segítette az antibiotikum választást az önök által a laboratóriumtól kapott mikrobiológiai lelet ?

❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5

67. Tapasztalt olyat, hogy a mikrobiológiai lelet félrevezető volt ?

❑ Igen ❑ Nem

Gyógyszertár szerepe

A következő kérdések az intenzív terápiás osztályra vonatkoznak

68. A gyógyszertári jelentéseken/számlákon feltüntették-e **2006**-ban külön az intenzív osztály által az
antibiotikumokra költött összeget ?

❑ Igen ❑ Nem

69. Volt-e 2006-ban az Önök intenzív osztályán bizonyos keretösszeg a gyógyszerek (és így az antibiotikumok) rendelésére ?

❑ Igen ❑ Nem

70. Volt-e példa 2006-ban arra, hogy pénzügyi hiány miatt nem tudták a leginkább megfelelő antibiotikumot megrendelni?

❑ Igen ❑ Nem

71. Hogyan történt 2006-ban az antibiotikum rendelés a gyógyszertártól?

❑ osztályra szólóan, elektronikusan

❑ osztályra szólóan, megrendelő lappal
❑ betegre szólóan, külön antibiotikum rendelő lappal
❑ betegre szólóan, gyógyszerrendelő lappal
❑ betegre szólóan, elektronikusan
❑ Egyéb :_____

72. Amennyiben betegre szólóan történt az antibiotikum rendelés, hány napra elegendő antibiotikumot lehetett rendelni egy alkalommal a gyógyszertárból ?

❑ 1 nap ❑ 3 nap ❑ 5 nap ❑ Több, mint 5 nap ❑ Nincs limitáció

73. Az indító, sürgősségi készleten túl volt-e több napra elegendő antibiotikum készlet az intenzív osztályon ?

❑ Igen ❑ Nem

74. Terápiás tanács kérhető volt-e munkaidőben a gyógyszerésztől ?

❑ Igen ❑ Nem

75. Terápiás tanács kérhető volt-e munkaidőn kívül a gyógyszerésztől ?

❑ Igen ❑ Nem

76. A napi viziteken rendszeresen jelen volt-e/segített-e e terápiát a gyógyszerész ?

❑ Igen ❑ Nem

77. Milyen gyakran kértek tanácsot a gyógyszerésztől az antibiotikum alkalmazással kapcsolatban?

❑ Naponta többször ❑ Naponta ❑Hetente ❑ Havonta ❑ Soha

78. Biztosított-e a gyógyszertár/gyógyszerész az elmúlt 3 évben a költségeken túl bármilyen visszajelzést a az antibiotikum felhasználásról?

❑ Igen ❑ Nem

79. Ha igen (78. kérdés) az mire irányult ?

❑ Gyakorisági jellemzők (pl. betegek hány százaléka kapott antibiotikumot)
❑ Nyers mennyiségi jellemzők (pl. dobozszámban kifejezett karbapenem fogyás 2 különböző időszakban)
❑ Standardizált mennyiségi jellemzők (pl. napi átlagos felnőtt dózisra az ún. Defined Daily Dose -DDD-re vonatkoztatott fogyás, pl. DDD/100 ápolási napban kifejezett antibiotikum fogyás)
❑ Minőségi jellemzők (pl. mennyire tartják be az irányelv egyes pontjait)

Gyógyszerforgalmazók szerepe

A következő kérdések az intenzív terápiás osztályra vonatkoznak, **2006-ra**

80. A gyógyszercégképviselőknek engedélyezve volt-e, hogy gyógyszermintákat hagyjanak az intenzív terápiás osztályon?

    ❑ Igen ❑ Nem

81. Kapott-e tájékoztatást a gyógyszertártól az intenzív terápiás osztály az aktuális antibiotikum rabatokról ?

    ❑ Igen ❑ Nem

82. Ha igen, meg tudná-e becsülni (1-5 ig skálán, 1=abszolút nem ; 5= kifejezetten) hogy az antibiotikum rabatok milyen mértékben támogatták gazdaságilag munkájukat ?

    ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5

83. Ön szerint az osztályán a racionális antibiotikum felhasználás mivel lenne még javítható?

    ❑ osztályon dolgozó orvosok továbbképzése
    ❑ ha eddig nem volt, mikrobiológus bevonása
    ❑ ha eddig nem volt, infektológus bevonása
    ❑ ha eddig nem volt, gyógyszerész bevonása
    ❑ felírási jog szűkítése
    ❑ egyéb : _____

Az intenzív osztály jellemzése

84. Milyen korosztályú betegeket fogadott 2006-ban az Önök intenzív osztálya ?

    ❑ felnőtt betegek
    ❑ gyermek betegek
    ❑ újszülöttek

85. Hány ággyal mükődött az intenzív osztály **2006**-ban ? _____ágy

86. Hány beteget látott el az intenzív osztály **2006**-ban ? _____beteg

87. Az összes **ápolási nap** száma az intenzív osztályon **2006**-ban : _____ápolási nap

88. A kardiológiai megfigyelő (koronária őrző) együtt mükődött-e **2006**-ban az Önök intenzív osztályával ?

    ❑ Igen ❑ Nem

89. Hány százalékát tették ki a **2006**-os osztályos betegforgalomnak a következő betegtípusok :

    ❑ Belgyógyászati: ___%
    ❑ Általános sebészeti: ___%
    ❑ Szívsebészeti: ___%
    ❑ Baleseti sebészeti: ___%
    ❑ Neurológia ___%
    ❑ Beavatkozást, lélegeztetést nem igénylő, kardiológiai megfigyelésen (koronária őrző) lévő betegek : ___%
    ❑ Egyéb típusú: ___%

90. Hány százelékát tették ki a **2006**-os osztályos betegforgalomnak a posztoperatív, rövid (<36h) ápolási idejű betegek :___%.

91. Az osztály **2006**-os Case-Mix-Indexe (az adat elérhető a kórház finanszírozási/kontrolling osztályán) : _____

92. Hány szakorvos dolgozott az osztályon **2006**-ban ? _____szakorvos

93. Hány szakvizsgával még nem rendelkező orvos dolgozott az osztályon **2006**-ban ? _____orvos

94. Hány rezidens orvos dolgozott az osztályon **2006**-ban ? _____rezidens orvos

95. Az összes orvos közül hány dolgozik több, mint 10 éve az osztályon ? _____orvos

96. A következő szakvizsga típusokkal hányan rendelkeznek az osztályon dolgozó orvosok közül ?

- ❑ aneszteziológia és intenzív terápia : _____orvos
- ❑ infektológia : _____orvos
- ❑ egyéb, megnevezve : _____orvos
- ❑ egyéb, megnevezve : _____orvos

97. Státuszban lévő orvosok átlagéletkora *:* _____év

Köszönjük, hogy kitöltötték a kérdőívet!

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