ANALYSIS OF HUNGARIAN HOSPITAL ANTIBACTERIAL USE FROM DIFFERENT ASPECTS

Ph.D. thesis

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2009

University of Szeged
Department of Clinical Pharmacy

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ABBREVIATIONS

ARPAC	Antibiotic Resistance Prevention and Control project
ATC	Anatomical Therapeutic Chemical
AUC	Area under the serum/plasma concentration–time curve
BAL	Bronchoalveolar lavage
CFU	Colony forming unit
CL	Levofloxacin clearance
CL_{CR}	Estimated creatinine clearance
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum serum/plasma drug concentration (peak)
CMI	Case Mix Index
C_{min}	Minimum serum/plasma drug concentration (though)
CPIS	Clinical Pulmonary Infection Score
DDD	Defined Daily Dose
DU90%	Drug Utilisation 90% segment
DURG	Drug Utilisation Research Group
ESAC	European Surveillance of Antimicrobial Consumption
f (prefix)	Free fraction
ICU	Intensive Care Unit
LOS	Length of stay
MIC	Minimum inhibitory concentration
OGYI	National Institute of Pharmacy
PAE	Post antibiotic effect
pBAL	Protected bronchoalveolar lavage
PD	Pharmacodynamic
PDD	Prescribed daily dose
PE	Pharmacoepidemiology
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
QEAs	Quantitative endotracheal aspirates
RDD	Recommended daily dose
SAPS II score	Simplified Acute Physiology Score II
SD	Standard deviation
ss (subscript)	At steady-state conditions
T	Time
$T_{1/2\beta}$	Elimination half-life
VAP	Ventilator-associated pneumonia
V_d	Volume of distribution
WHO	World Health Organization

PUBLICATIONS RELATED TO THE THESIS

Papers

I. **R Benko**, M Matuz, P Doro, E Hajdu, G Nagy, E Nagy, Gy Soos: [Antibiotic consumption between 1996 and 2003: national survey and international comparison]. *Orv Hetil* 2006; 147(26): 1215-1222.

II. **R Benko**, M Matuz, P Doro, R Viola, E Hajdu, DL Monnet, G Soos. Hungarian Hospital Antibiotic Consumption at the regional level, 1996-2005. *Infection*. 2009; 37(2): 133-137. **IF_{2006}: 2.368**

III. **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* [under publication]

IV. **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**

V. **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

VI. **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.

VII. **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.

VIII. **R Benko**, M Matuz, E Hajdu, M Dominique, Gy Soos: A magyarországi ambuláns és kórházi antibiotikum felhasználás területi különbségei. Magyar Infektológiai és Klinikai Mikrobiológiai Társaság 36. Kongresszusa. Abs: *Infektológia és Klinikai Mikrobiológia* XV. 15 Suppl 1. S14, 2008

IX. **R Benko**, M Matuz, A Hegedus, Z Peto, Gy Soos, L Bogar, E Hajdu: 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

X. **R Benko**: Levofloxacin plazmaszint mérésen alapuló terápiás hatáselemzés kritikus állapotú betegekben. Magyar Infektológiai és Klinikai Mikrobiológiai Társaság 2007. évi Pályázatának előadásai és eredményhirdetése, Budapest, 2007

XI. **R Benko**, M Matuz, E Hajdu, Z Peto, A Molnar, J Gardi, E Nagy, Gy Soos. Pharmacokinetics of intravenous levofloxacin in critically ill patients with ventilator-associated pneumonia 8th Congress of Chemotherapy and Infection&4th European Conference on Viral Diseases, Budapest, 2006

XII. **R Benko**, M Matuz, P Doro, R Viola, Gy Soos: Hungarian Hospital Antibiotic Consumption. Does It Matter Which Measure? 22nd International Conference on Pharmacoepidemiology &Therapeutic Risk Management, Lisbon, 2006. Abs: *Pharmacoepidemiol Drug Saf* 15,S1, P614, 2006

XIII. **R Benko,** M Matuz, E Hajdu, G Nagy, E Nagy, P Doro, A Toth, E Kosik, Gy Soos: Regional differences in hospital and community antibiotic consumption in Hungary, ESCP 5th spring conference on Clinical Pharmacy, Stockholm, Sweden, 2005

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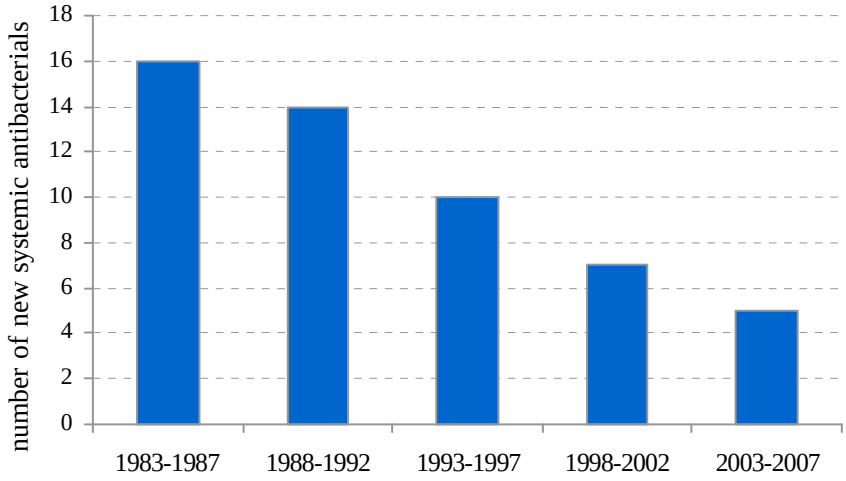
1. INTRODUCTION

The discovery of antimicrobial agents is considered to be one of the ten great public health achievements of the twentieth century [1,2]. These agents have played a pivotal role in the management and control of infectious diseases and in the decrease in infectious disease related mortalities [1,3]. Initially, antibacterials were seen as truly miraculous drugs and considered the ‘‘panacea’’ of Medicine, but nowadays the evolution of drug-resistant organisms has greatly impaired their therapeutic efficacy [4-9]. Although antimicrobial resistance has been recognized since the earliest days of antibiotic therapy (it developed rapidly in some bacteria after the first use of penicillin), the process has accelerated and compounded during the last two decades and is now reaching alarming levels in certain pathogens and certain geographical regions [8,10-15].

The causes of antimicrobial resistance are complex and multi-factorial in nature [15,16]. Firstly, antimicrobial resistance is a naturally occurring biological phenomenon driven by Darwinian natural selection [17]. Hence it is an inevitable accompaniment of appropriate antibiotic use [18]. However, accumulated evidence points to misuse of antibacterials having further amplified the emergence and spread of antibacterial resistance [6,16,18-21]. The antimicrobial resistance crisis is heightened by the concomitant downward trend in the intent of pharmaceutical companies to develop novel antimicrobials [22-24]. As a consequence only a limited number of new antibacterial drugs have been introduced into the market in the last three decades [22,23,25] (Figure 1).

Figure 1. Systemic antibacterial new molecular entities approved by the United States Food and Drug Administration [25].



Antibiotics are one of the most commonly used medicines in hospitals and have substantial share from the hospitals' budget [26-36]. As their inappropriate use has both medical (increased risk of side-effects, therapeutic failure), economic (financial burden) and public health consequences (selection of resistance) substantial efforts are needed to rationalise their use.

Before designing any interventions aiming to optimise antibiotic use, data collection and evaluation is needed to identify problematic fields. At international level, the European Surveillance of Antimicrobial Consumption (ESAC) project is tasked with collecting reliable antibiotic use data.

The use of drugs could be evaluated not only at general population level but also at individual patient level. During my Ph.D. work I intended to follow these steps: to apply pharmacoepidemiologic methods to investigate features and trends of hospital antibacterial consumption in Hungary and to evaluate the individual antibiotic therapy in critically ill patients by using the pharmacokinetic/pharmacodynamic concepts.

2. BACKGROUND

2.1. *Pharmacoepidemiology*

A modern definition of pharmacoepidemiology (PE) is "the study of the utilisation and effects (beneficial and adverse) of drugs in large numbers of people" [37]. Pharmacoepidemiology as a post-marketing study is used to assess how drugs function in the 'real world': it describes, explains and forecasts the use and effects of pharmacologic treatments in a defined time, space and population [38,39]. PE can be viewed as a bridge science, spanning both pharmacology and epidemiology (i.e. application of epidemiological methods to pharmacological matters) [40]. Traditionally PE has dealt with data from populations, but now it is quite often based on clinical data acquired via a bedside approach. Thus, pharmacoepidemiology also has much in common with the discipline of clinical pharmacology [39].

The principal aim of pharmacoepidemiologic research is to enhance the rational and cost-effective use of medications in the population [37]. PE can be divided into two main fields: one includes studies of side effects, adverse drug effects, and post marketing studies investigating long-term effects of specific drugs in a population. The other - drug utilisation studies – was defined by World Health Organization (WHO) as the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences [41]. More recently, drug utilisation research has been defined as an eclectic collection of descriptive and analytical methods for the quantification, understanding and evaluation of the process of prescribing, dispensing and consumption of medicines and for testing of interventions to enhance the quality of these processes [42]. Practically, drug utilisation studies may provide insights to the pattern of drug use (e.g. the extent, the trends), can assess the quality of use, identify predictors for use and generate explanatory hypotheses [37,39].

Collecting data on different aspects of drug use is a prerequisite to be able to initiate a discussion on rational drug use or to suggest measures to improve it. Ideally, all drug policy decisions should be based – and regularly re-evaluated– on comprehensive drug utilisation data [43,44]. It is important to keep in mind that although drug utilisation studies can contribute to rational drug use by identifying the areas that require attention and action, but in itself, does not necessarily offer the solutions for the problems [37].

2.1.1. The history of drug utilisation studies and the Drug Utilisation Research Group

The field of drug utilisation research has roots back to the 1960s, when early drug utilisation studies were performed in Northern Europe and the United Kingdom [45]. During this early work, international comparisons were impossible, due to the application of different units and methods to measure drug use. Soon after this pioneering work, at a seminal symposium in Oslo (entitled the "Consumption of Drugs", 1969), organized by the WHO Regional Office for Europe, researchers expressed the need for a common classification system for drugs as well as a technical unit of comparison in drug utilisation studies [46]. To overcome this difficulty, scientists mainly from Northern European countries came together in an informal group and developed a new unit of measurement, initially called the agreed daily dose [47], and later the defined daily dose (DDD) [48,49]. Another important methodological development was the introduction of the uniform Anatomical Therapeutic Chemical (ATC) classification system in the mid-1970s [49]. The small group of scientists active in these areas established the informal Drug Utilisation Research Group (DURG) in 1976. As the WHO Regional Office for Europe served as its secretariat, this group was often referred as WHO-DURG for about 20 years.

The first publication applying the ATC/DDD principles appeared in 1975 [47], while from 1981, the ATC/DDD system was proposed for drug utilisation studies. To maintain and develop the ATC/DDD system, the WHO Collaborating Centre for Drug Statistics Methodology was established in 1982 in Oslo [43,49]. In 1996, the WHO realized that the ATC/DDD system should be implemented and used outside of Europe as well, and the expert panel of WHO International Working Group for Drug Statistics Methodology was founded to facilitate the globalization of the ATC/DDD system.

By 1993, the relationship between DURG and WHO has loosened as the later was unable to further support the DURG with secretarial functions. Therefore in 1994 an independent EuroDURG (European Drug Utilisation Research Group) interim committee was elected, while in 1996, at a meeting at Lake Balaton, the EuroDURG was formally established [50,51]. Since the 1996 meeting at Balatonaliga, there has been EuroDURG meeting practically every year, most of them organised jointly with the European Association of Clinical Pharmacology and Therapeutics (EACPT) or the International Society of Pharmacoepidemiology (ISPE).

The contribution of WHO-DURG/EuroDURG and its members to these conferences and drug utilisation research itself has been substantial [42,52,53].

2.1.2. The Anatomical Therapeutic Chemical (ATC) system

In the ATC classification system, drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological, and therapeutic properties. Drugs are classified in groups at five different levels where a seven digit code identifies a unique active agent. The structure of the code is illustrated by the complete classification of levofloxacin:

J	Antiinfectives for systemic use (1st level, anatomical main group)
J01	Antibacterials for systemic use (2nd level, therapeutic subgroup)
J01M	Quinolone antibacterials (3rd level, pharmacological subgroup)
J01MA	Fluoroquinolones (4th level, pharmacological/chemical subgroup)
J01MA12	Levofloxacin (5th level, chemical substance)

Medicinal products are classified in the ATC system according to their main therapeutic indication of their main active ingredient. An active ingredient can be classified under more than one ATC codes, if it is marketed in different strength and/or formulation with clearly different therapeutic uses (e.g. oral and rectal metronidazole: P01AB01; intravenous metronidazole: J01XD01 [37]).

2.1.3. Drug utilisation metrics, concept of the defined daily dose (DDD)

The defined daily dose (DDD) is an internationally accepted technical unit in drug utilisation studies. It means the assumed average maintenance dose per day for a drug used for its main indication in adults. It should be emphasized that the DDD does not necessarily correspond to the recommended-, or actually prescribed daily dose (RDD and PDD) [37].

Drug utilisation figures should ideally be standardized. The DDDs per 1,000 inhabitants and per day is the most widely used measurement unit, mainly applied for ambulatory care drug consumption data. When drug use in hospitalised patients is considered, the number of DDDs per 100 patient-days is the WHO recommended technical unit [37], while the number of DDDs per 100 admissions is an optional, complementary unit [54].

Although the DDD per 100 patient-days is the WHO recommended measure of hospital drug use that allows international comparison [37,55], its limitations should be emphasised. First, different studies may use different definitions for the length of stay or fail to report the definition (e.g. [56-66]) which could greatly affect the value of the denominator (i.e. patient-days) and hence the resulting drug consumption value. Due to this, the applied calculation method (e.g. whether days of admission and discharge count together as one or two patient-days) should be clearly stated

[67,68]. Secondly, drug utilisation studies rarely assess the precise amount of drug ingested by or administered to the patients [69,70]. They provide an upper or lower estimation of real drug use, depending on the data source they are derived from (prescribed quantity, distributed quantity, dispensed quantity, reimbursed quantity).

Although the WHO intends to keep the number of alterations to minimum, it is important to be aware that the ATC/DDD index is a dynamic system to which changes are made continually [37]. For enhancing the meaningful comparisons of drug consumption data, the applied version of the ATC/DDD index should be also indicated in the published data. As concerns the antibiotics more than 30 DDD changes have been made since 1982.

Table 1. DDD alterations of systemic antibacterials (J01) between 1982−2009

Substance	Previous DDD		New DDD		Year changed
Amoxiclav[1]	1	g P	3	g P	2005
Azlocillin	6	g P	12	g P	1991
Benzylpenicillin	2	MU P	3.6	g P[2]	1991
Cefaclor	2	g O	1,5	g O	1992
Cefaclor	1.5	g O	1	g O	2000
Cefaloridine	2	g P	3	g P	1992
Cefamandole	2	g P	6	g P	1992
Cefatrizine	2	g O	1	g O	2000
Cefazolin	2	g P	3	g P	1992
Cefepime	4	g P	2	g P	2000
Cefoperazone	2	g P	6	g P	1992
Cefoperazone	6	g P	4	g P	2000
Cefotaxime	2	g P	6	g P	1992
Cefotaxime	6	g P	4	g P	2000
Cefotetan	2	g P	4	g P	1992
Cefotiam	2	g P	4	g P	1992
Cefoxitin	2	g P	6	g P	1992
Cefradine	3	g O,P	2	g O,P	1992
Cefsulodin	4	g P	6	g P	1992
Cefsulodin	6	g P	4	g P	2000
Ceftazidime	4	g P	6	g P	1992
Ceftazidime	6	g P	4	g P	2000
Ceftezole	6	g P	3	g P	2008
Ceftizoxime	2	g P	4	g P	1992
Cefuroxime	2	g O	1	g O	1992
Cefuroxime	2	g P	4	g P	1992
Cefuroxime	1	g O	0.5	g O	2000
Cefuroxime	4	g P	3	g P	2000
Ciprofloxacin	1	g P	0.5	g P	1992
Erythromycin	1	g O	2	g O[3]	1990
Fosfomycin	4	g P	8	g P	1992
Levofloxacin	0.25	g O,P	0.5	g O,P	2004
Ofloxacin	0.3	g O	0.4	g O	1993
Pipemidic acid	2	g O	0.8	g O	1993
Teicoplanin	0.2	g P	0.4	g P	1994

DDD: defined daily dose; g: gram; MU: million unit; O: Oral; P: parenteral, [1] amoxicillin and clavulanic acid; [2] 3.6 g benzylpenicillin corresponds to 6 MU; [3] only valid for erythromycin ethylsuccinate tablets

2.1.4. Antibacterial drug utilisation studies in Hungary

The Ministry of Health 12/1978 ordinance appointed the National Institute of Pharmacy (OGYI) to execute the adaptation of the ATC/DDD system, and to collect national drug utilisation statistics in Hungary. Beside the official drug utilisation duties of the OGYI, only a few researchers have taken the initiative within the country and have carried out drug utilisation studies [71]. Despite the low interest in performing drug utilisation studies, antibacterials had received special attention and lots of works were published mainly in the 80's and 90's [3,33,35,36,44,72-98].

Some of these works report antibiotic use in ambulatory care [73,83,91,95,96], some of them in hospital care [33,35,36,74-82,85,87-90,92,99,100], some works analysed antibiotic use in both sectors [72,85,86,98] and some of the works reported overall antibiotic use [3,44,84,93,94,97]. Whilst these are very valuable pioneering pieces of research, some criticisms may be levelled at them, particularly concerning essential methodological information. The lack of ATC classification to group antibacterials or simply the lack of clear defining of agents included in the study as antibacterials [3,33,35,36,44,44,72,74-80,85,87-93,97,98,100] were general problems. If DDD or its standardized form (e.g. DDD per 100 patient-days) were the measurement units, the information about the used DDD version and/or the source and calculation method of the denominator (e.g. patient-days) were also lacking in many cases which might hamper meaningful comparisons [3,36,44,72,73,84,87,88,89,93-95,98]. There were cases when disclosure of raw data source were incomplete [36,84,86,88,89,98] and there was also a case when arbitrary own DDDs were defined [77]. Some of these methodological problems were also identified in other European countries reporting antibacterial use [101].

As concerns antibacterial consumption in the hospital care sector, several published works reveal very valuable, sophisticated features of antibiotic use (e.g. number of patients receiving antibiotics, rate of empiric/targeted antibiotic therapy, diagnoses related antibiotic use, etc.) [33,35,74-76,78-81,87,92,98]. However, the number of works that applied the ATC/DDD methodology and expressed hospital antibiotic use in DDD or DDD per 100 patient-days is scarce [36,72,77,88-90]. There has been only one study by Graber which applied the ATC/DDD methodology and provided national coverage of hospital antibacterial drug use in Hungary for 1990-1996 [72]. Therefore, the drug utilisation research performed in this thesis was motivated on the following considerations:

- Systemic antibacterials have a key role among hospital drugs (i.e. frequent prescription of antibiotics, substantial share from hospital drug budget) [26-36]
- The number of Hungarian studies that use standardized drug consumption units for hospital antibacterial use is limited [36,72,77,88-90]
- Recent published data on hospital antibacterial use in Hungary is lacking
- In Hungary, the regional distribution of hospital antibiotic use and its possible determinants have not been studied so far
- Although intensive care units are the epicentres of the hospital antibiotic use, drug utilisation studies are scarce from Hungary [76,87,89,90,98], and only two of these from the ‘80s and 90’s applied the ATC/DDD methodology [89,90].

2.2. *Optimal antibacterial use: the role of pharmacokinetics and pharmacodynamics*

2.2.1. Rationale for optimal dosing

Rational antibiotic therapy through appropriate selection and dosage regimens can be viewed as a strategy to enhance patient safety by achieving the desired outcome and minimizing the risk of toxicity. In many infections, the ultimate goal of antibiotic therapy is not simply to guarantee clinical success but to achieve it through a total bacteriological cure [102,103].

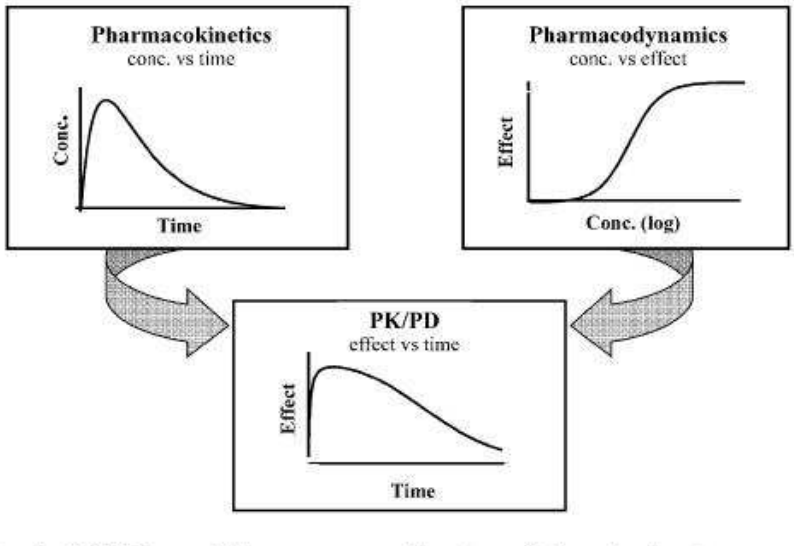
If bacterial eradication does not occur, less susceptible bacteria are likely to head the recolonization process after discontinuation of therapy and a more resistant population will become predominant [104]. Since the repeated exposure to suboptimal concentrations of antibiotics has been found to be the most important risk factor for selection of resistant bacteria [105-107], the role of appropriate dosing has gained further value. In summary, optimal dosing regimens of antibiotics will have an impact not only on patients' outcome and cost, but it will reduce the risk of resistance development.

2.2.2. The pharmacokinetic/pharmacodynamic (PK/PD) concept

Although soon after the discovery of penicillin, Eagle and co-workers observed the relationship between the therapeutic efficacy of penicillin and its concentration in the serum [108-110], this knowledge however was never really implemented in dosing strategies. Only during the last two decades has renewed interest in this field clarified the importance of pharmacokinetic and pharmacodynamic to the appropriate dosing of antibiotics. The selected, most important pharmacokinetic and pharmacodynamic parameters are defined [111-113] and summarized in the annex (section 10.1. on page 60).

The pharmacokinetic/pharmacodynamic (PK/PD) model is a mathematical concept that links pharmacokinetics and pharmacodynamics. The goal of this approach is to describe, predict, and if possible understand the time course of the antibiotic effect as a function of the drug dosage regimen (Figure 2).

Figure 2. Pharmacokinetic/pharmacodynamic (PK/PD) modelling as a combination of the classic pharmacological disciplines pharmacokinetics and pharmacodynamics [114]



In general, two important factors predict bacterial killing in-vivo, and thus, clinical and bacteriologic outcomes: the drug exposure achieved in an individual patient (PK) and the minimum inhibitory concentration (MIC) of the antibacterial agent to the bacteria causing the infection (PD) [113]. With the PK/PD approach we can address these two main sources of inter- and intra-individual variability in therapy outcome and we can perform the dual adaptation of the antibiotic regimen: adjustment for variations in both antibiotic availability (PK) and bacterial susceptibility (PD) [115].

2.2.3. The pharmacokinetic/pharmacodynamic (PK/PD) indices

Both animal and human experiments indicate that the relationship between pharmacokinetics and pharmacodynamics (PK/PD) can be used to predict the bacteriologic efficacy of antimicrobials. The large numbers of studies conducted in this field allow us to define and use the PK/PD properties of many antibiotics in order to optimise their antibacterial effect.

Antibiotics can be divided into three groups [116]:

1. those that exhibit concentration-dependent killing and prolonged post antibiotic effect (PAE)
2. those that exhibit time-dependent killing and minimal to moderate PAE
3. those with time-dependent killing and prolonged PAE

Aminoglycosides, fluoroquinolones, metronidazole and daptomycin fall into the first group. In this group higher drug concentrations result in more rapid and extensive organism killing and the area under the serum/plasma concentration-time curve (AUC) and maximum (peak)

serum/plasma drug levels (C_{max}) in relation to the MIC of the causative pathogen (AUC/MIC ratio and C_{max}/MIC ratio, respectively) are the major PK/PD indices correlating with efficacy.

Beta-lactams are belonging to the second group where extending the duration of exposure optimizes antimicrobial activity. For this group of antibacterials the time the serum/plasma concentration of the antibiotic remains above the MIC (T>MIC) is the PK/PD index determining the in-vivo efficacy.

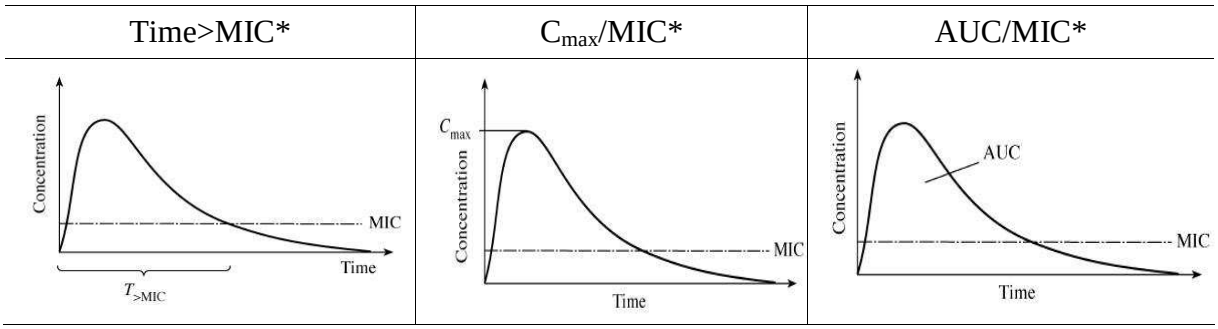
The third pattern of activity is observed for glycopeptides, linezolid, quinupristin/dalfopristin and the glycylcyclines. In this case higher antibacterial concentrations do not enhance organism killing but produce prolonged suppression of organism regrowth. The goal of dosing with these drugs is to optimize the amount of drug. The AUC/MIC ratio is the index most closely associated with efficacy.

Table 2. Patterns of antibacterial activity and corresponding pharmacokinetic/pharmacodynamic (PK/PD) indices

Pattern of antibacterial activity	Concentration dependent bacterial killing	Time dependent bacterial killing	Concentration dependent bacterial regrowth inhibition
Examples	aminoglycosides, fluoroquinolones	cephalosporins, carbapenems	glycopeptides, linezolid
PK/PD parameter correlating with efficacy	AUC/MIC; C_{max}/MIC	T>MIC	AUC/MIC

AUC: area under the serum/plasma concentration-time curve; C_{max}: maximum serum/plasma drug concentration; MIC: minimum inhibitory concentration; T > MIC: time that serum/plasma levels remain above the MIC

Figure 3. Pharmacokinetic/pharmacodynamic (PK/PD) parameters correlating with efficacy [117]



AUC: area under the serum/plasma concentration-time curve; C_{max}: maximum plasma/serum drug concentration; MIC: minimum inhibitory concentration; T > MIC: time that serum/plasma levels remain above the MIC

Before analysing in detail the PK/PD properties of fluoroquinolones it is necessary to note that only the free or unbound fraction of the drug is responsible for the antibacterial effect [118,119]. Most clinical pathogens are located extracellularly. If there is no barrier (e.g. blood brain barrier) to impede drug diffusion, the free antibiotic concentration in the plasma approximates its free concentration in the extracellular space. Therefore the free drug concentration in plasma is the best drug-related predictor of clinical success even for tissue infections [120-124] and it must be considered when examining the relationship between PK parameters and in-vivo activity [111]. If not the free antibacterial fraction is meant, the degree of protein binding should be stated in such a way that the concentration of the unbound fraction of the drug can be readily calculated [111].

2.2.4. Pharmacokinetic/pharmacodynamic (PK/PD) indices determining the efficacy of fluoroquinolones

There is now general consensus that the clinical and microbiological outcomes of fluoroquinolone treatment are favourable and selection of a mutant subpopulation is preventable if at least an AUC/MIC≥100–125 and a C_{max}/MIC of ~10 are achieved in Gram-negative infections [125-129]. For Gram-positive pathogens, the minimum required C_{max}/MIC is also 10, whilst there is no complete agreement about the optimum AUC/MIC target values [125,130,131]. An AUC/MIC of 30–50 is claimed to be optimal in numerous studies performed mainly in vitro or animal models [132-139]. Other studies conducted on different patient populations suggested a minimum AUC/MIC of 87–125 to achieve a favourable outcome and to avoid development of resistance regardless of whether the organism is Gram-positive or Gram-negative [129,131,140].
In my opinion, these higher PK/PD target values, derived from human studies should be used when the in-vivo efficacy of fluoroquinolones are considered in patients.

2.2.5. Optimising antibacterial dosing in a clinical setting

The best scenario would be the use of PK parameters directly obtained from the individual patient and obtain the MIC (PD parameter) of the organism causing the infection. However in the everyday clinical practise this approach is not feasible. Therefore the PK/PD indices should be calculated on the basis of local epidemiology (MIC 90 of the suspected organism: see section 10.1. on page 60 for definition) and pharmacokinetic studies pertaining to the target population (e.g. ICU patients).

In this thesis, I set out to determine the pharmacokinetic/pharmacodynamic variables of a fluoroquinolone agent in intensive care unit (ICU) patients with ventilator-associated pneumonia. The selection of the patient population, the infection type and the evaluated antibacterial (levofloxacin) were motivated by the following facts:

- Ventilator-associated pneumonia (VAP) is the most frequent intensive care unit (ICU)-acquired infection, accounting for 30–50% of all ICU infections [141-143]
- Levofloxacin's antibacterial spectra covers most of the organisms recovered from ICU patients, therefore proposed for the treatment of multiple infectious diseases in this setting [130]
- The number of reported studies on patients with VAP and treated with levofloxacin is still limited, and only two with very different objectives have been published so far [144,145]
- Despite the fact that pharmacokinetics of antimicrobial drugs are often altered in ICU patients [146,147], the number of studies addressing the pharmacokinetics of levofloxacin in critically ill subjects is low and based on measurements of total drug levels [144,148-153] or limited to patients with renal replacement therapy [154-158].

3. MAIN RESEARCH OBJECTIVES

3.1. *Drug utilisation studies*

1) To analyse the changes in the amount and structure of antibacterial consumption in the hospital care sector in Hungary between 1996 and 2007.
2) To explore possible regional variations and investigate determinants of antibiotic consumption in hospital care in Hungary.
3) To show antibiotic related activities in Hungarian adult intensive care units and in their parent institute and analyse antibiotic use of Hungarian adult intensive care units (preliminary study).

3.2. *Pharmacokinetic study*

1) To analyse the pharmacokinetics and pharmacodynamics of levofloxacin in critically ill patients with ventilator-associated pneumonia.
2) To study the associations between pharmacokinetic and patient-related parameters.
3) To evaluate the theoretic pharmacokinetic/pharmacodynamic (PK/PD) appropriateness of different levofloxacin regimens.

4. METHODS

4.1. *Drug utilisation studies*

Similar to other drug utilisation publications, in the present dissertation the term ‘drug use’, ‘drug utilisation’ and ‘drug consumption’ are synonyms and are used interchangeably. All statistical analyses in this section were performed with SPSS (version 15). A P value less than 0.05 was considered as statistically significant.

4.1.1. National and regional hospital antibiotic consumption

Retrospective analysis of distribution data (from wholesalers to hospitals) was performed on a 12-year period (1996-2007) for systemic antibacterials (i.e. ATC group J01). For the whole country and for each Hungarian region (county), yearly crude data were kindly provided by the IMS PharmMIS Consulting Company. This dataset means 100 % hospital coverage. Hospital consumption includes data from chronic care institutions (e.g. rehabilitation centres) but does not include data from nursing homes or any use for outpatients (e.g. hospital’s out-patient departments). Product classification and defined daily dose (DDD) calculations were performed according to the 2008 version of the WHO ATC/DDD index [159].

Hospital-specific antibiotics (selected antibiotics mainly used in the hospital sector) were defined, as previously proposed by the European Surveillance of Antibiotic Consumption (ESAC) project, as third- and fourth-generation cephalosporins, carbapenems, monobactams (note: monobactams are not available in the Hungarian market), aminoglycosides, and glycopeptides [160].

Data on number of patient-days were obtained from the database of the National Health Fund Administration [161]. In these data the days of admission and discharge are counted together as one patient-day. Patient-days from chronic care institutions were included in these data.

National and regional hospital antibiotic consumption was expressed in DDD per 100 patient-days. To enable international benchmarking with the ESAC data in the discussion we also expressed antibiotic use data in DDD per 1,000 inhabitants and per day. A linear regression (trend analysis) was set up to investigate the trends in the national hospital antibiotic utilisation through the study period. Additionally, the top-list of antibacterials and the number of active agents accounting for 90% of the total hospital

antibacterial use (i.e. DU90% segment) were determined as proposed by Bergman [162]. The DU90% method ranks drugs by volume of DDD and set the cut-off where the cumulative percentile share of the ranked drugs reaches the 90% of total use.

4.1.2. Regional variations of hospital antibiotic consumption and its determinants

To assess the interregional variation in antibiotic consumption on the above (section 4.1.1) mentioned dataset, the maximum/minimum (max/min) ratio was calculated. The relative use of different antibacterial groups, the top-list of antibacterials and the number of active agents in the DU90% segment was also compared between regions [162]. To investigate the determinants for regional differences in hospital antibiotic consumption, we applied multiple linear regression method similar to Filippini et al. [163]. The following possible determinants were retrieved and evaluated:

Variables related to	Available independent variables
Health care access	number of beds per 10,000 inhabitants
Utilisation of hospital resources	number of hospital admissions per 10,000 inhabitants, average length of stay
Doctors' workload	number of patient-days per one hospital physician
Type of hospital care provided	percentage of active patient-days, percentage of patient-days in surgical units, percentage of patient-days in intensive care or infectious disease units
Patient's characteristics and infections	case mix index[1], percentage of admitted cases aged 65 years or older, number of reported infections per 100 patient-days

[1]case mix index (CMI): economic parameter that serves as a basis for hospital reimbursement. It is an easily available index calculated using diagnoses-related groups and shows severity of illness.

Data on independent variables were extracted from two databases [161,164] directly maintained by or relying on data reported to the Hungarian National Health Fund Administration. As independent variables were available only for 2004 or 2005, the antibiotic use data for the corresponding years was used in the multiple linear regression [165].

Additionally, we tested the association between hospital and ambulatory care antibiotic consumption in Hungarian regions with Pearson correlation test. For this purpose the regional level ambulatory care antibiotic consumption data was obtained for 2004 and 2005 (wholesale data from IMS PharmMIS) and expressed as DDD per 1,000 inhabitants and per day. Demographic data on each county were obtained from the yearbook of the Hungarian Central Statistical Office [166]. Normal distribution of regional antibacterial use (both hospital and ambulatory) was proved by Shapiro-Wilks test.

4.1.3. Antibiotic related activities in Hungarian adult ICUs and in their parent institute

To assess the antibiotic related activities of Hungarian adult intensive care units (ICUs) and their parent institutes a retrospective questionnaire study was performed. In this dissertation I focus on answers related to hospital committees, certain elements of antibiotic policies, antibiotic related educations, surveys on antibiotic use, information sources used to guide antibiotic therapy and the involvement of hospital pharmacists. (Data on some elements of antibiotic policy (e.g. existence of restricted antibiotic list) can be found only in the section (5.1.5) where antibiotic use in Hungarian ICUs is analysed). Data on some unit and patient characteristics (e.g. type of patients, number of patient-days, case-mix index, etc.) were also provided in the questionnaire.

Our team (ICU specialists, microbiologist/infectologists; pharmacists) developed and validated the questions. In the questionnaire development the survey of the ARPAC (Antibiotic Resistance Prevention and Control) project was used as a template. Questionnaires were sent both electronically and via normal post to the head of adult Hungarian ICUs in December 2007.

4.1.4. Antibiotic use in Hungarian adult intensive care units

We intended to collect systemic antibiotic consumption data (i.e. ATC group J01) for those Hungarian ICUs who sent back the above mentioned (section 4.1.3.) questionnaire. Hospital pharmacies were contacted and asked to provide package level antibiotic use data dispensed to their corresponding ICUs during 2006. Crude data was converted into DDDs [159] and finally expressed as DDD per 100 patient-days (days of admission and discharge counted together as one patient-day). Hospital specific antibiotics were defined in section 4.1.1., on page 14.

All submitted data on antibiotic use was validated. Outliers and unexpected values were identified and ICUs, central pharmacy departments or controlling departments were contacted for clarification.

ICUs were classified to be surgical, medical or interdisciplinary based on the treated patient types. ICUs were also categorized according to the provided level of care (local, regional, tertiary care). The relationship between antibiotic use at ICUs and certain elements of antibiotic policy reported on the questionnaire or other possible influencing factors (e.g. ICU type, case-mix index) were also examined. To explore differences and relationships the analysis of variances (ANOVA) with Bonferonni post-hoc test or the Pearson correlation analysis was performed, as applicable.

4.2. *Pharmacokinetic study*

4.2.1. Study design and entry criteria

A prospective, open-label study was performed between September 2003 and December 2005 in a 6-bed neurotrauma ICU. The protocol was previously approved by the local Ethics Committee (section 10.2. on page 61). Fourteen ICU patients, in whom intravenous levofloxacin therapy was started and the following requirements were fulfilled, were enrolled:

- over 16 years of age
- suspected ventilator-associated pneumonia (VAP), defined as a Clinical Pulmonary Infection Score (CPIS) ≥ 6
- informed consent obtained from the closest relative
- the renal function was normal as defined by an estimated creatinine clearance (CL_{CR}) > 50 mL/min, based on the Cockroft-Gault formula
- presence of intra-arterial and central venous lines in situ

CPIS calculation was different from the original [167] as quantitative culturing was performed instead of semi-quantitative and were scored as follows: protected bronchoalveolar lavage (pBAL) $\geq 10^3$ colony forming units (CFU)/mL; quantitative endotracheal aspirates (QEAs) or bronchoalveolar lavage (BAL) $\geq 10^5$ CFU/mL was scored with 2 points; in other cases the score was zero. Patients were excluded from the study if they developed a renal insufficiency with an estimated CL_{CR} of < 50 mL/min, were on dialysis; or they had received levofloxacin within 2 weeks prior to study recruitment.

4.2.2. Drug administration and sample collection

Levofloxacin (2×500 mg on the first day and 1×500 mg on consecutive days) was administered as an intravenous infusion for 60 min through a central venous catheter. Samples for levofloxacin plasma concentration determinations were obtained from an arterial line under steady-state conditions. Blood samples were collected in heparinized glass tubes (BD Vacutainer system) before the infusion and 30, 60 min; and 2, 4, 6, 8, 12, 18, and 24 h after the start of the infusion and were promptly separated (centrifugation at 4 ºC). Plasma was transferred to labelled polypropylene test tubes and kept frozen at -70 ºC until assayed. The concentrations of free levofloxacin in the plasma were determined by high-pressure liquid chromatography (HPLC) after minor in-house modifications and validation of a previously developed method [168]. For removing plasma proteins the

thawed samples were transferred to a Centrifree Micropartition Device (Millipore, Bedford, MA) and centrifuged at 2000g (50 min, 37 ºC). The assay was linear over the standard curve concentration range from 0.13 to 16.67 mg/L. The levels of precision, expressed as inter- and intraday coefficients of variation, were < 10%. The lower limits of detection and quantification were 0.04 mg/L and 0.13 mg/L, respectively.

4.2.3. Pharmacokinetic and statistical analysis

In the present study all pharmacokinetic terms were used in accordance with the updated terminology [111]. Individual patient plasma concentration−time data were analysed by a two-compartment open model with first-order elimination, using the WinNonLin software package (version 5.1, Pharsight Corp., Mountain View, CA, USA). The following parameters were determined: the elimination half-life ($T_{1/2\beta}$), the volume of distribution (fV_d) and the total body levofloxacin clearance (CL). The steady-state area under the free plasma concentration−time curve over 24 hours (fAUC) determination was based on the linear trapezoidal rule. The maximum free plasma concentration at steady state ($fC_{max,ss}$), and the minimum free plasma concentration at steady state ($fC_{min,ss}$) were observed directly as the concentrations at the end of the infusion and at 24 h (just before the next dose), respectively.

Statistical analysis was performed with the SPSS program package. For continuous variables the normal distribution was tested by the Kolmogorov-Smirnov test. The possible association between pharmacokinetic (fAUC, $fC_{max,ss}$ and CL) and different patient parameters (weight, age, CL_{CR}, SAPS II score, administration of diuretic drugs) were tested by multiple linear regression. P values below 0.05 were considered statistically significant.

4.2.4. Efficacy assessment

The pharmacokinetic/pharmacodynamic (PK/PD) appropriateness of levofloxacin therapy was assessed by calculating the two most relevant PK/PD indices: the $fC_{max,ss}$/MIC and the fAUC/MIC [116,117,125,127,131]. The target values - reported by various studies - for these PK/PD parameters are discussed in the background section (section 2.2.4.). In this dissertation I used an AUC/MIC target of 100-125 for both Gram-negatives and Gram-positives, as these higher PK/PD target values were derived from human studies and they are more relevant in the context of this dissertation.

As the PK/PD ratios – used as target values in the present study – were set up using total drug levels [127,129,140], the $fC_{max,ss}$ and fAUC values were also corrected for protein binding (assuming 31% bound fraction) in these calculations and were indicated as $C_{max,ss}$ and AUC.

Although only a limited number of patients were enrolled in this study, both clinical and microbiological outcomes were assessed.

Clinical signs and laboratory data used for setting up diagnosis (incorporated in CPIS score) were evaluated at the conclusion of the therapy as follows:

- Cure: disappearance of all signs and symptoms related to the infection
- Improvement: a marked reduction in the severity and/or number of signs and symptoms of infection
- Failure: deterioration or the absence of improvement of the clinical signs.

Microbiological efficacy:

- Eradication: a previously positive culture of a clinical sample became negative and remained negative upon continued culturing
- Failure: the lack of complete eradication of the original organism
- Superinfection: during or immediately after the end of therapy there was growth of a new organism that was judged to be causing an infectious process.

Microbiological samples were analysed quantitatively, and cytological inspection was carried out to reveal the presence of neutrophil granulocytes and intracellular bacteria. Bacterial isolates were identified on species level using standard methods. Susceptibility to relevant antibiotics (including levofloxacin) prior to therapy was tested by the disc diffusion technique according to the standards of the Clinical and Laboratory Standards Institute (CLSI) [169]. The MICs of the different causative pathogens for levofloxacin were determined later, by the E-test method (AB Biodisk, Solna, Sweden).

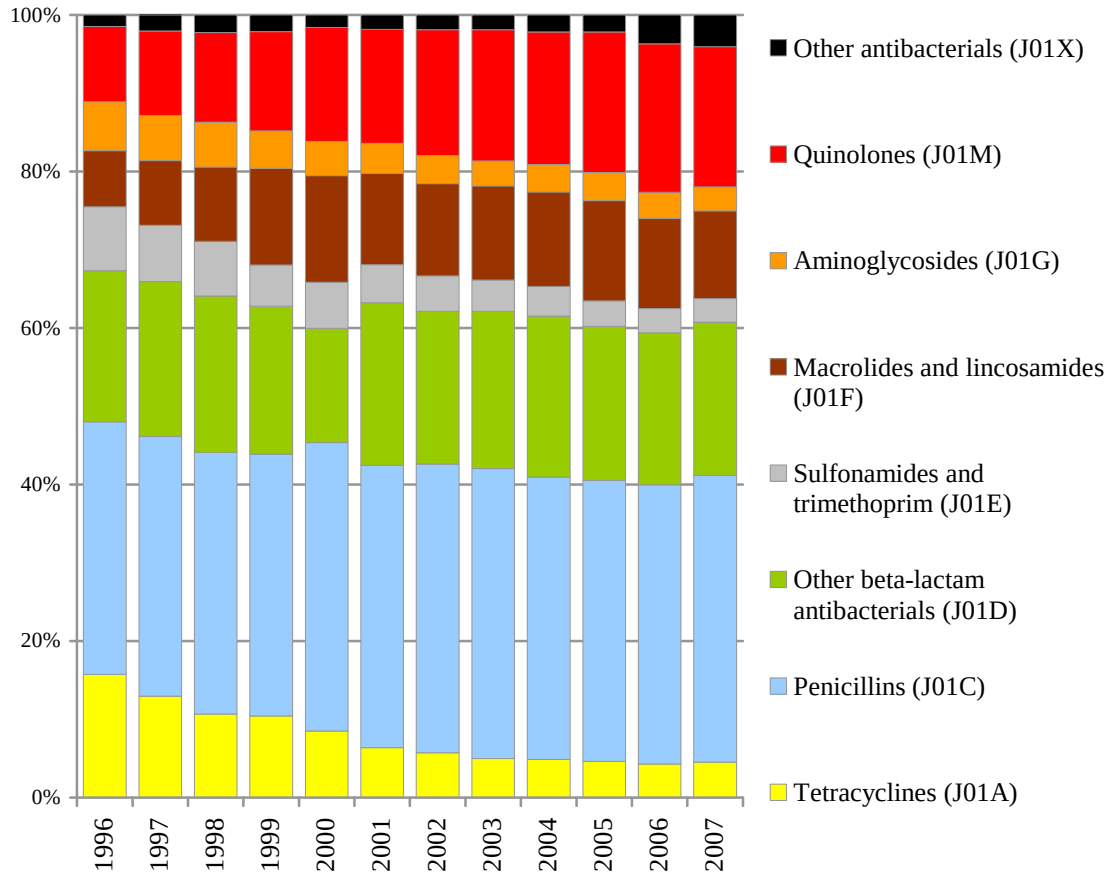
5. RESULTS

5.1. *Drug utilisation studies*

5.1.1. National trends in antibacterial utilisation

National hospital antibiotic consumption in total number of DDDs has decreased by 27 % (from 6.16 to 4.48 million DDDs) between 1996 and 2007. As the total number of hospital patient-days has also decreased by 24 % (from 25.50 million to 19.28 million patient-days) the standardized consumption unit remained relatively stable during the period 1996-2007 (mean ± standard deviation: 22.0 ± 1.7 DDD per 100 patient-days). In each year hospital-based antibiotic use accounted for 6.0−8.2 % of the total national consumption. The gradual change in the pattern of hospital antibiotic use can be followed on Figure 4.

Figure 4. Distribution of main antibiotic groups in the total hospital antibiotic consumption



The results of the trends analysis and the top 10 list of antibacterials with their relative share from total hospital antibiotic use can be followed in Table 3 and Figure 5, respectively. In this section all values in the text in parentheses refer to the two endpoints of

the study: 1996 and 2007. The use of tetracyclines diminished to less than one-third of the original value and in parallel, their usage share also decreased considerably (Table 3 and Figure 4). Among all antibacterials the penicillin plus beta-lactamase inhibitors (ATC code: J01CR) were inevitably the most important: both their overall use (Table 3) and their share from total penicillin use (40.6 % vs. 85.8%) rose considerably. The co-amoxiclav (i.e. amoxicillin and clavulanic acid) combination was the number one antibacterial in every year except 1996, with more than a 2.5-fold increase in use (from 2.8 to 7.0 DDD per 100 patient-days) during the 12 years of assessment. All other penicillin groups displayed a significant drop in use (Table 3). At the first part of the study the second-generation cephalosporins accounted for the bulk consumption of cephalosporins, while by 2007, the third generation cephalosporins has played as important role as second generation agents (Table 3). Cefuroxime was the most popular cephalosporin agent through the whole study period (Figure 5).

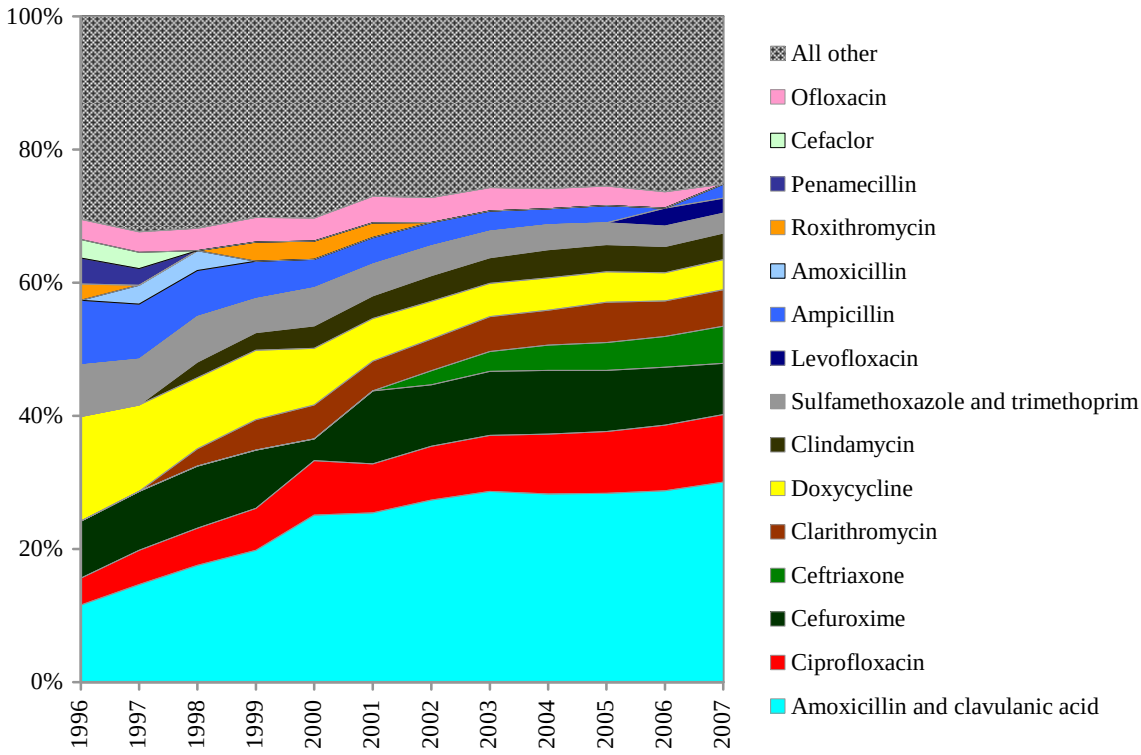
Table 3. National consumption of antibiotics in hospitals (DDD per 100 patient-days) in 1996 and 2007 (A) and results of the trend analysis for the 12 years of assessment (B)

	A			B	
Antibacterial group	1996	2007	% Change[c]	Correlation coefficient (R)	P value
J01 Systemic antibacterials	24.14	23.28	-3.56	0.040	0.901
J01A Tetracyclines	3.80	1.06	-71.96	0.890	<0.001
J01CA Penicillins with extended spectrum	3.09	0.90	-70.74	0.878	<0.001
J01CE Beta-lactamase-sensitive penicillins	1.51	0.31	-79.82	0.886	<0.001
J01CF Beta-lactamase-resistant penicillins	0.03	0.06[a]	82.73	0.837	0.009
J01CR Penicillin combinations including beta-lactamase inhibitors	3.16	7.32	131.37	0.974	<0.001
J01DB First-generation cephalosporins	0.24	0.25	5.06	0.257	0.421
J01DC Second-generation cephalosporins	3.34	1.97	-41.02	0.609	0.036
J01DD Third-generation cephalosporins	1.02	1.98	95.37	0.928	<0.001
J01DE Fourth-generation cephalosporins	0.03[b]	0.04	36.10	0.510	0.161
J01DH Carbapenems	0.07	0.31	343.45	0.962	<0.001
J01E Sulfonamides and trimethoprim	1.98	0.70	-64.63	0.929	<0.001
J01FA Macrolides	1.30	1.68	28.96	0.363	0.246
J01FF Lincosamides	0.43	0.93	118.47	0.973	<0.001
J01G Aminoglycoside antibacterials	1.51	0.72	-52.05	0.837	0.001
J01M Quinolones	2.32	4.17	79.91	0.961	<0.001
J01XA Glycopeptide antibacterials	0.05	0.19	250.77	0.932	<0.001
J01XD Imidazole derivatives	0.30	0.44	47.47	0.209	0.515
Parenteral antibiotics	6.39	7.35	15.02	0.452	0.140
Hospital specific antibiotics[d]	2.65	3.25	22.64	0.574	0.051

[a]: data from 2003 (products were withdrawn from the market in the second half of 2003); [b]:data from 1999 (products are available from 1999);[c]: percentage change as a percentage of the start value (1996);[d]:Hospital-specific antibiotics: third- and fourth-generation cephalosporins, carbapenems, monobactams, aminoglycosides, and glycopeptides.

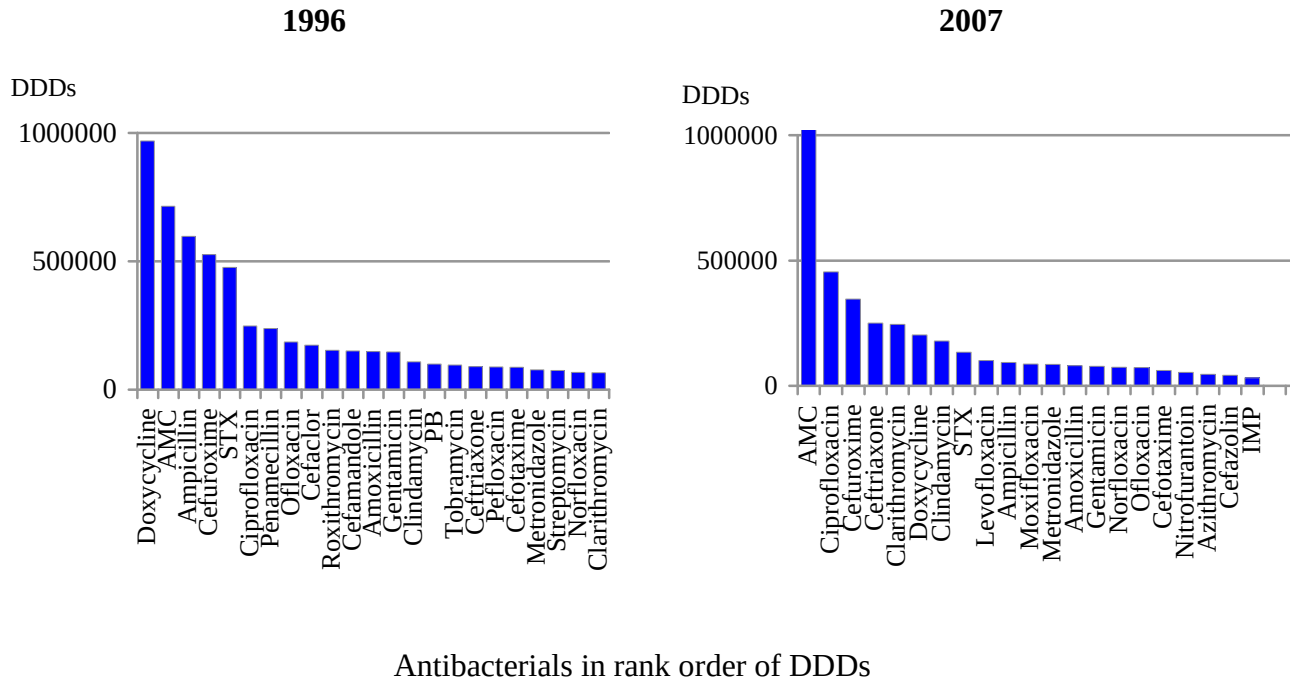
Carbepenems exhibited a significant increase in use (Table 3). By 2007 the use of meropenem and imipenem plus cilastatin were almost identical (0.14 vs. 0.16 DDD per 100 patient-days), while the new agent's, ertapenem's role has remained marginal. The hospital usage of the sulfonamides fell to one third (Table 3) during the study period (these values were displayed erroneously in our article published in the Orvosi Hetilap). The relative share of macrolides and lincosamides has increased, mainly in the first few years of the study (Figure 4). Overall, the aminoglycosides became less commonly used, only the less toxic agent, amikacin showed a positive trend in use. The fluoroquinolones gained an extended usage in the hospital care, its most prominent representative, ciprofloxacin consumption doubled (0.97 vs. 2.36 DDD per 100 patient-days; see also Figure 5). Ofloxacine also showed a considerable use and was among the top 10 antibacterials until 2006, when a respiratory fluoroquinolone, levofloxacin replaced it in the top-list (Figure 5). As concerns glycopeptides, we observed a 3-fold increase in the use of vancomycin (0.05 vs. 0.15 DDD per 100 patient-days).

Figure 5. The relative share of the top 10 antibacterials from total hospital antibacterial use in Hungary, 1996-2007



The heterogeneity of antibacterial use was evaluated by means of the DU90% segment method [162]. As it can be observed on Figure 6, the national hospital use of antibacterials became less colourful by 2007 with the high dominance of co-amoxiclav use.

Figure 6. Antibiotics and their consumption in DDDs in the DU90% segment



AMC: amoxicillin and clavulanic acid, STX: sulfamethoxazol and trimethoprim, PB: procaine benzylpenicillin, IMP: imipenem and cilastatin

5.1.2. Regional differences in antibacterial utilisation

Despite the stable national standardized hospital antibacterial use, there were large variations depending on the region (Figure 7). For each year during 1996-2007, the difference between the regions with the lowest and the highest total hospital antibiotic consumption (expressed as maximum/minimum ratio) ranged between 1.8 and 2.6. Both at the start and end point of the study, all antibiotic classes showed a large interregional variation in their use with a maximum/minimum ratio above two (Table 4). These regional differences were also present when only the parenteral antibacterials or the so-called hospital-specific antibiotics were considered (Table 4). Not only the quantitative antibacterial use, but the pattern of use also differed considerable between the Hungarian regions (Figure 8, data shown for 2007). The relative share of tetracyclines showed the highest deviation: in 2007 its relative use ranged between 2.0 % and 11.3 %. The most prominent group, the penicillins recorded a relative use between 25.1 % and 49.2 % in 2007. Analysis at the active agent level revealed that the top 3 agents in 2007: co-amoxiclav, ciprofloxacin and cefuroxime exhibited a relative use of 20.7% to 39.3 %, 6.0 % to 14.1% and 2.4 % to 14.8 %, respectively, depending on the region.

Figure 7. Regional hospital antibiotic consumption (DDD per 100 patient-days) in Hungary

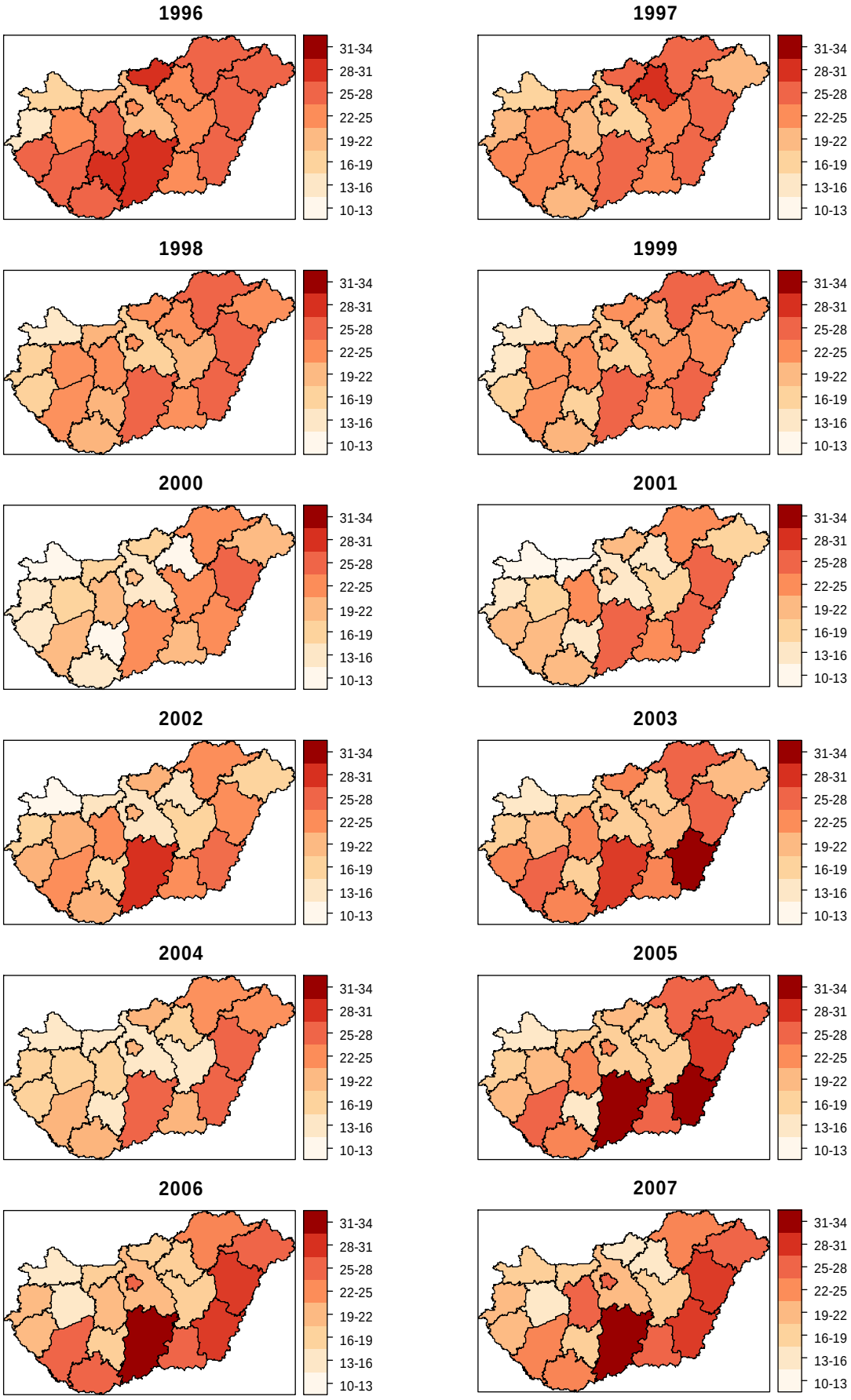
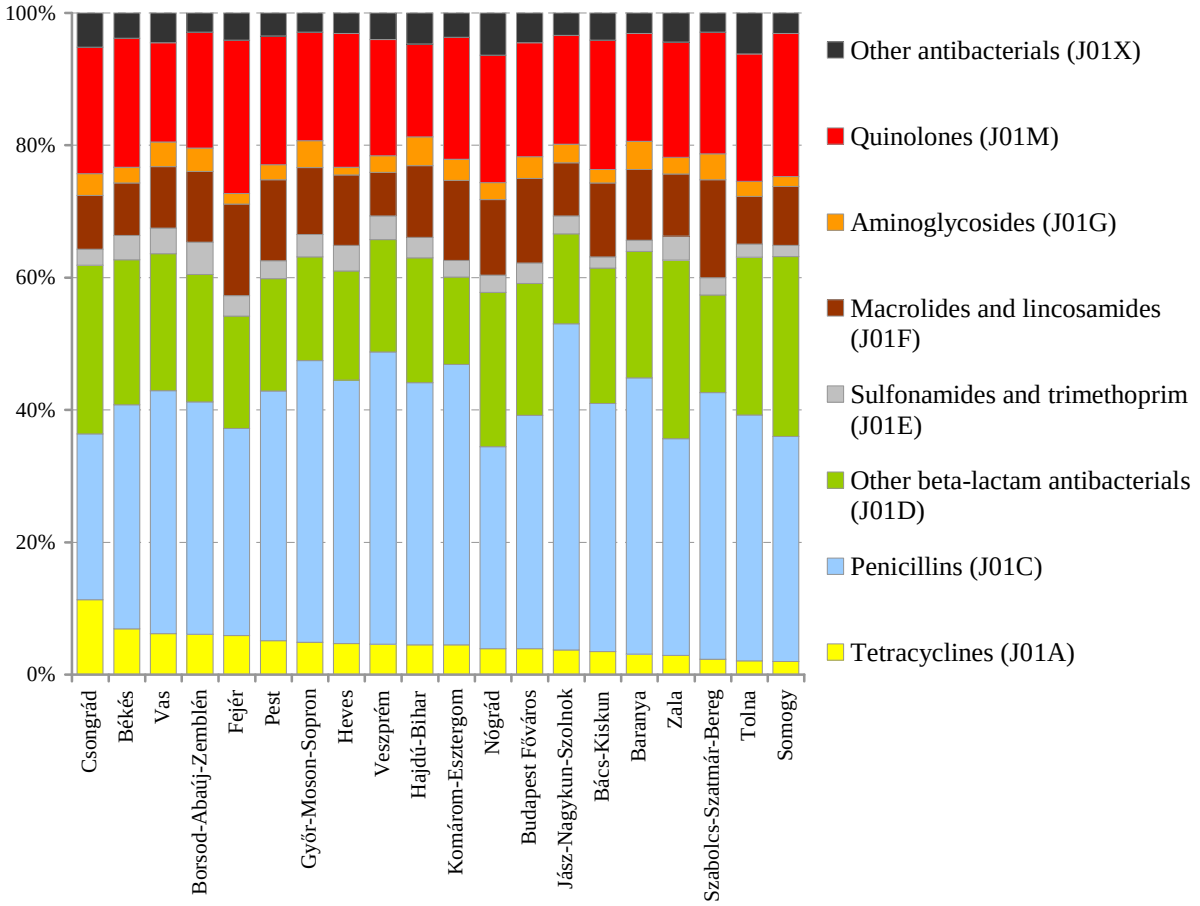


Table 4. Hospital antibiotic consumption of Hungarian regions (in 1996 and 2007)

Antibacterial group	1996 DDD per 100 patient-days				2007 DDD per 100 patient-days			
	Mean ± SD[a]	Min	Max	Ratio Max/Min	Mean ± SD[a]	Min	Max	Ratio Max/Min
J01 Systemic antibacterials	24.24±3.67	15.96	28.24	1.77	21.89±5.79	13.38	34.57	2.58
J01A Tetracyclines	3.88±0.99	2.27	6.31	2.78	1.04±0.64	0.34	3.13	9.12
J01CA Penicillins with extended spectrum	3.16±1.42	0.94	6.86	7.28	0.78±0.44	0.18	1.91	10.47
J01CE Beta-lactamase-sensitive penicillins	1.51±0.72	0.63	3.40	5.35	0.32±0.21	0.06	0.83	14.03
J01CF Beta-lactamase-resistant penicillins	0.03±0.03	<0.01	0.08	nc	[b]			
J01CR Penicillin combinations including beta-lactamase inhibitors	3.04±0.97	1.22	4.95	4.06	6.96±1.82	3.45	10.82	3.14
J01DB First-generation cephalosporins	0.28±0.16	0.03	0.59	22.88	0.21±0.14	<0.01	0.45	nc
J01DC Second-generation cephalosporins	3.43±1.17	1.60	6.54	4.10	1.99±1.03	0.63	4.60	7.34
J01DD Third-generation cephalosporins	1.01±0.48	0.39	2.23	5.78	1.88±0.76	0.69	3.83	5.58
J01DE Fourth-generation cephalosporins	[c]				0.04±0.03	<0.01	0.12	nc
J01DH Carbapenems	0.05±0.06	0.01	0.28	nc	0.23±0.15	0.04	0.59	14.29
J01E Sulfonamides and trimethoprim	2.05±0.51	1.25	2.97	2.37	0.63±0.23	0.31	1.15	3.65
J01FA Macrolides	1.28±0.35	0.77	2.22	2.89	1.45±0.64	0.52	2.93	5.58
J01FF Lincosamides	0.39±0.19	0.06	0.94	16.24	0.84±0.37	0.21	1.75	8.30
J01G Aminoglycosides	1.6±0.49	0.79	2.87	3.61	0.64±0.29	0.16	1.29	8.03
J01M Quinolones	2.18±0.62	0.94	3.11	3.30	4.01±1.21	2.59	6.77	2.61
J01XA Glycopeptide antibacterials	0.04±0.03	0.01	0.14	nc	0.15±0.09	0.06	0.33	5.28
J01XD Imidazole derivatives	0.30±0.13	0.06	0.54	9.62	0.45±0.2	0.15	0.88	5.74
Parenteral antibacterials	6.63±1.46	4.25	8.73	2.05	6.98±2.07	3.17	10.86	3.43
Hospital specific antibacterials[d]	2.70±0.78	1.60	4.20	2.63	2.93±1.05	0.96	4.96	5.15

[a]SD: standard deviation; [b]: not marketed in 2007;[c]: not marketed in 1996.; nc: ratio not calculated because of extreme low minimum value (min≤0.01), [d]:Hospital-specific antibiotics: third- and fourth-generation cephalosporins, carbapenems, monobactams, aminoglycosides, and glycopeptides.

Figure 8. Distribution of main antibiotic groups in the total hospital antibiotic consumption in Hungarian regions, 2007



The heterogeneity of antibiotic use also showed interregional differences: in 1996, the number of active agents in the DU90% segment ranged from 17 to 23; while in 2007 it ranged from 13 to 22. In the county (Heves) with 13 antibacterials in the DU90 segment in 2007 several antibacterial groups (e.g. first-generation cephalosporins, beta-lactamase-sensitive penicillin, penicillins with extended spectrum) were not represented in the DU90 segment, hence their use were marginal.

5.1.3. Determinants of regional hospital antibacterial use

Outputs of the multiple linear regression are summarized in Table 5. Two models were built: in Model 1 the entered variable was the number of reported infections, while in Model 2 the number of reported infections and the case mix index (CMI) determined hospital antibiotic use at regional level. Model 1 and Model 2 accounted for 53 % and 61% of the observed regional variations in hospital antibiotic consumption, respectively. Other variables were excluded from both models.

Table 5. Multiple linear regression parameter estimates for the two models

			Unstandardised Coefficients			Collinearity Statistics[a]	
Model	R Square[b]		Regression coefficient	Std. Error	P value	Tolerance	Variance Inflation Factor
1	0.537	Constant	7.19	2.14	0.00		
		No. reported infections[c] per 100 patient-days	13.52	2.04	0.00	–	–
2	0.615	Constant	-3.61	4.41	0.42		
		No. reported infections[c] per 100 patient-days	12.64	1.91	0.00	0.97	1.03
		Case-mix index	11.12	4.06	0.01	0.97	1.03

Excluded variables: number of beds per 10,000 inhabitants; number of patient-days per one hospital physician; percentage of active patient-days, percentage of patient-days in surgical units; percentage of patient-days in intensive care or infectious disease units; average length of stay; percent of admitted cases aged 65 years or older; number of hospital admissions per 10,000 inhabitants, years. Observations: 40

[a] It assess the independency of tested variables

[b] R-square (coefficient of determination): indicator of how well the model fits the data

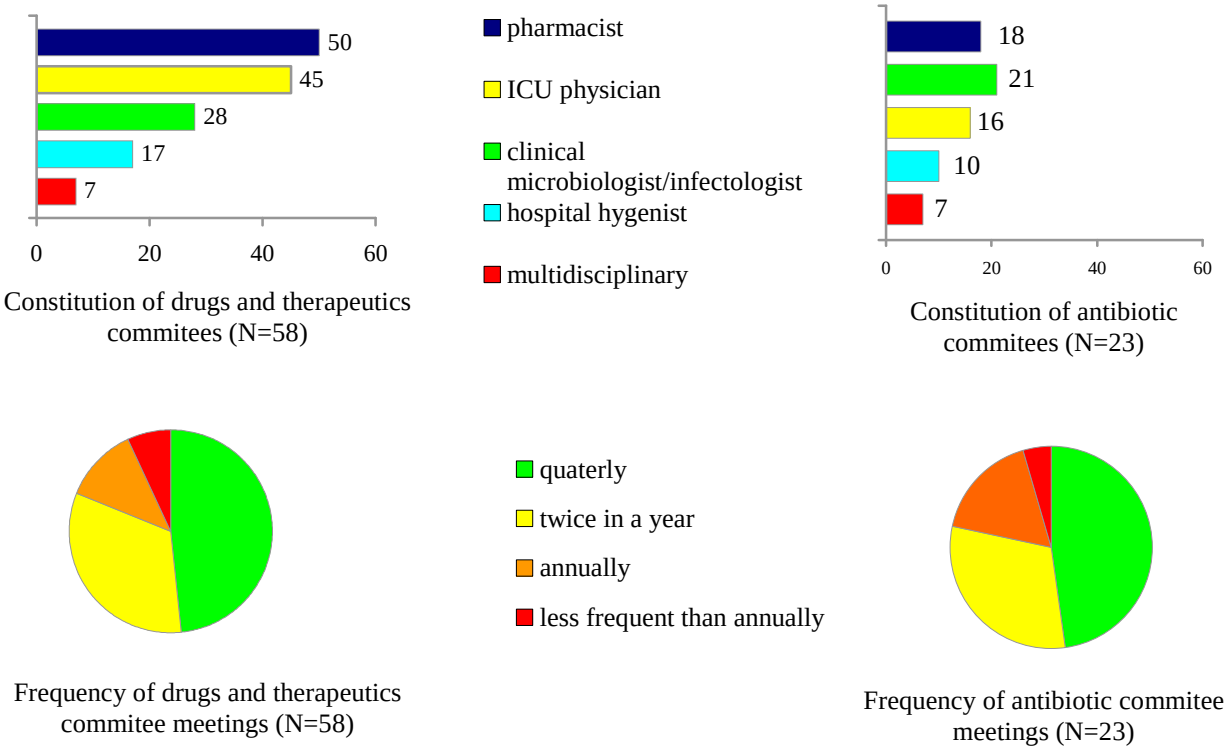
[c] Includes both hospital-acquired infections and community-acquired infections with hospital admission

In the Pearson correlation test, interestingly, total regional antibiotic consumption in hospitals showed a positive and significant association with total regional antibiotic consumption in ambulatory care (R=0.71, p=0.002).

5.1.4. Antibiotic related activities in Hungarian adult ICUs and in their parent institute

Responses were received from 60 Hungarian adult ICUs corresponding to a 62% response rate. Existence of drugs and therapeutics committee and separate antibiotic committee was reported in 58 (97%) and 23 (38%) hospitals, respectively. The involvements of different professions are summarized in Figure 9. Pharmacists were members of these committees in 50 (86%) and 18 cases (78%), respectively. As concerns antibiotic therapy, multidisciplinary team – involvement of intensive care physician, clinical microbiologist/infectologist, hygenist and pharmacist were realized in 7-7 hospitals (12%) and (30%) (Figure 9). In half of the hospitals the frequency of these committee meetings was twice a year or even less frequently (Figure 9).

Figure 9. Constitution of hospital committees and frequency of their meetings



Constitution of drugs and therapeutics commitees (N=58)

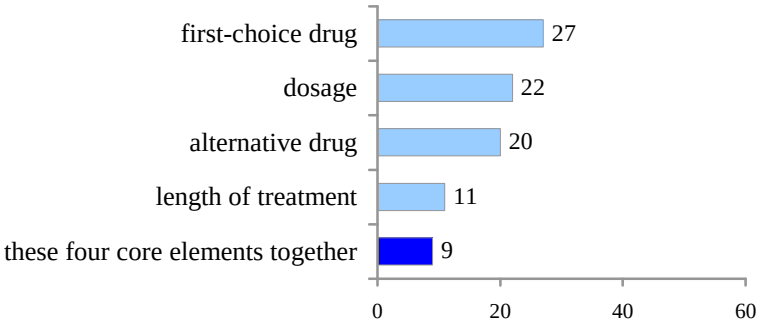
Constitution of antibiotic commitees (N=23)

Frequency of drugs and therapeutics commitee meetings (N=58)

Frequency of antibiotic commitee meetings (N=23)

Written antibiotic policy and guideline for empiric antibiotic therapy was available in 27 (45%) ICUs. These guidelines were worked out in only 13 places (48%) by hospital committees. Pharmacists were involved in these guideline developments in 11 cases (41%). The four core information elements of guidelines (first-choice drug, alternative drug, dosage, length of treatment) were indicated in 9 cases (Figure 10).

Figure 10. The information content of empiric guidelines

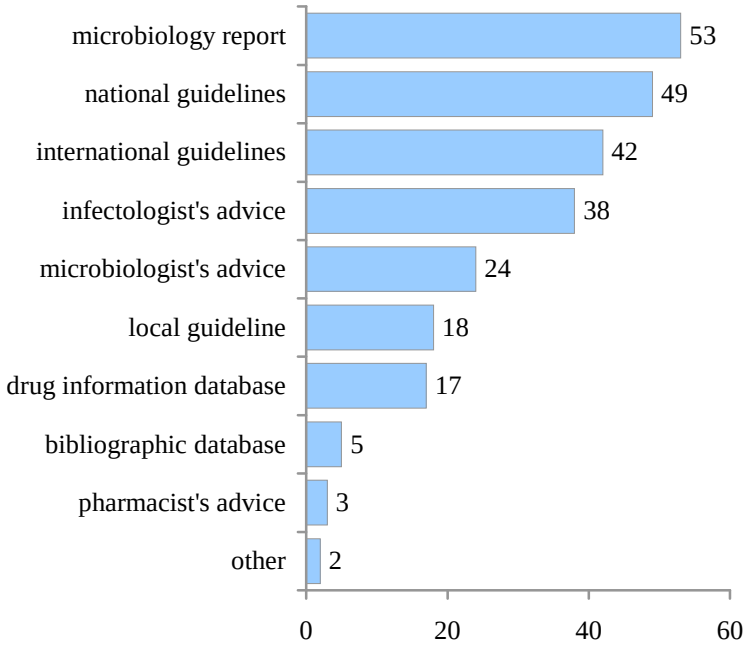


For guiding antibiotic treatment the microbiological laboratory reports and national/international guidelines served usually as a basis, whilst among the three most useful information sources the

microbiology report, national guidelines and the infectologist's advice were listed most often (Figure 11). The pharmacists played a marginal role as information sources.

Figure 11. Type of information sources used (A) and judged to be among the three most useful (B) in guiding antibacterial treatment

A



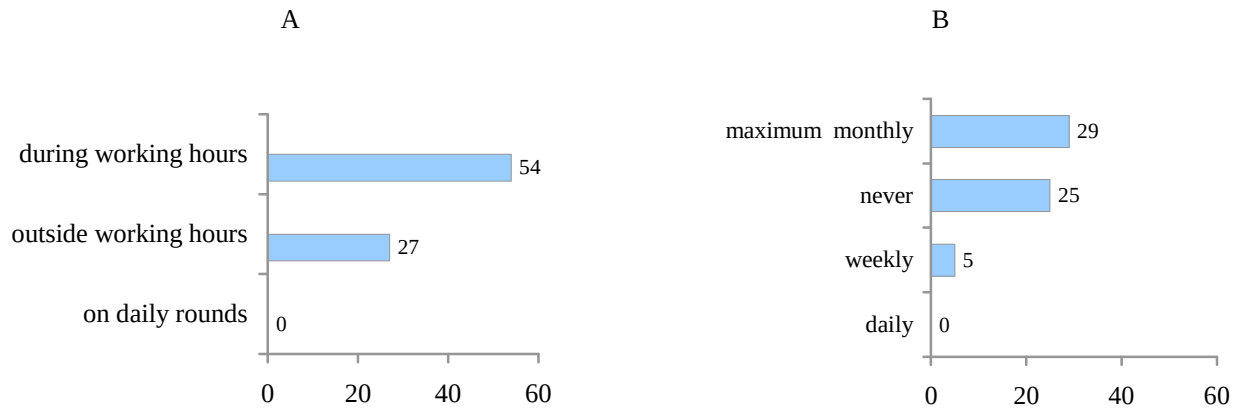
B

microbiology report	45
national guidelines	37
infectologist's advice	31
international guideline	19
microbiologist's advice	13
local guidelines	12
drug information database	6
pharmacist's advice	1
bibliographic database	1
other	1

Locally organized education on antibiotic use was performed in 35 ICUs (58%); education on both antibiotic use and consequences of resistance development was performed in 26 ICUs (43%) in the two years before completing the questionnaire. Pharmacists were involved in 3 cases (9%), pharmaceutical companies in 14 cases (40%) of these educational sessions. Continuous education on antibiotic use was realized in three ICUs (9%), while the efficacy of education sessions was surveyed in 4 ICUs (11 %). Statistics on antibiotic use were performed in 33 units (55%). Financial aspects, frequency of antibiotic use, quality of antibiotic use and crude measure of quantitative antibiotic use (i.e. number of packages) were surveyed at 22, 20, 15 and 6 ICUs, respectively. Standardized antibiotic use expressed in DDD per 100 patient-days was calculated in case of only 5 ICUs (8%). Prescribers received personal feed-back on the results of the antibiotic use survey only in one ICU.

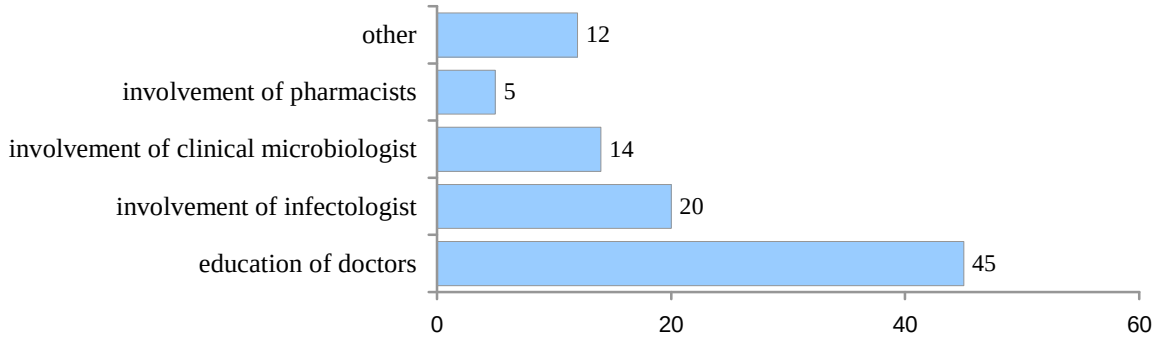
As concerns the ward level activities of pharmacists, we found that they participated in daily rounds in none of the units. Most units never or maximum monthly ask the pharmacists about antibiotics, despite of their good availability (Figure 12).

Figure 12. The availability of pharmacists (A) and the frequency of pharmacist consultations on antibiotics (B)



Improvement of antibiotic use is believed to be reached by education of doctors (45 answers, 75%). Only 5 units (8%) indicated that involvement of a pharmacist might help in rationalising antibiotic use in the future (Figure 13).

Figure 13. The believed ways of rationalising antibiotic use in ICUs



Other: restricted prescribing authority (3), antibiotic responsible personnel (1), obtaining a bronchoscope (1), more rapid microbiology report turnover (1), better availability of microbiology laboratory (1), increased number of microbiological samples (1), common education sessions with related departments (e.g. traumatology) (1), audit of microbiology results (1)

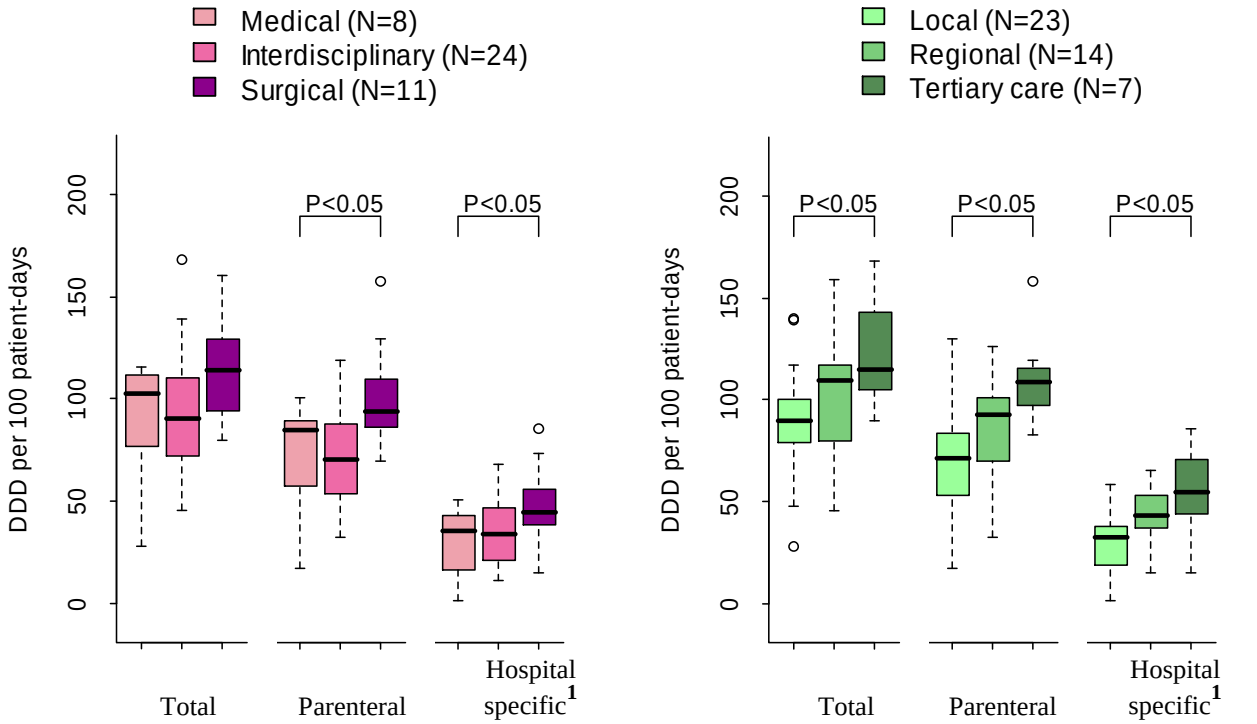
5.1.5. Antibiotic use in Hungarian adult intensive care units

Out of the 60 ICUs who participated in the questionnaire survey, 49 were able to provide crude antibiotic use data for 2006. During the validation process, 5 ICUs was excluded from the analysis. Seven out of the remaining 44 ICUs were located in tertiary care hospitals, 14 in regional hospitals and 23 in local hospitals. ICUs were surgical (n=11), medical (n=8) and interdisciplinary (n=24). One ICU did not provide data on the type of admitted patients hence it could not be categorized. The median number of beds per ICU was 8 (range 6–22) and the mean number of admissions per

ICU was 445 in 2006. The case mix index ranged between 2.80 and 16.34 with a median of 5.18. Mean (± standard deviation) length of stay was 5.25±1.74 days.

A total of 92476 DDDs and 95086 patient-days were included in the analysis. Consumption of systemic antibacterials varied widely, ranging between 27.91 and 167.79 DDD per 100 patient-days and with a median of 97.66 and mean of 98.69 DDD per 100 patient-days. The proportional use of parenteral agents at Hungarian ICUs ranged from 46.15 to 98.30 % of total antibacterial use (average: 81.03%, median: 83.51%). In highest quantities the co-amoxiclav, ciprofloxacin and moxifloxacin products were used orally. In surgical ICUs slightly higher total antibacterial use and significantly higher parenteral and hospital specific antibiotic use were detected. Significant differences in total, parenteral and hospital specific antibiotic use were also found between ICUs with different category (i.e. level of care; Figure 14.)

Figure 14. Boxplot of antibiotic use stratified by ICU type and ICU category



1:Hospital-specific antibiotics: third- and fourth-generation cephalosporins, carbapenems, monobactams, aminoglycosides, and glycopeptides

The mean of overall antibiotic use was highest for penicillins with beta-lactamase inhibitors, followed by quinolones and third generation cephalosporins (Table 6). Similar ranking were detected in interdisciplinary and surgical ICUs. In medical ICUs the consumption of quinolones out-ranged other classes of antibacterials (Table 6). Stratifying by ICU type also showed differences in the use of second generation cephalosporins and glycopeptides which were used in higher quantities in surgical ICUs.

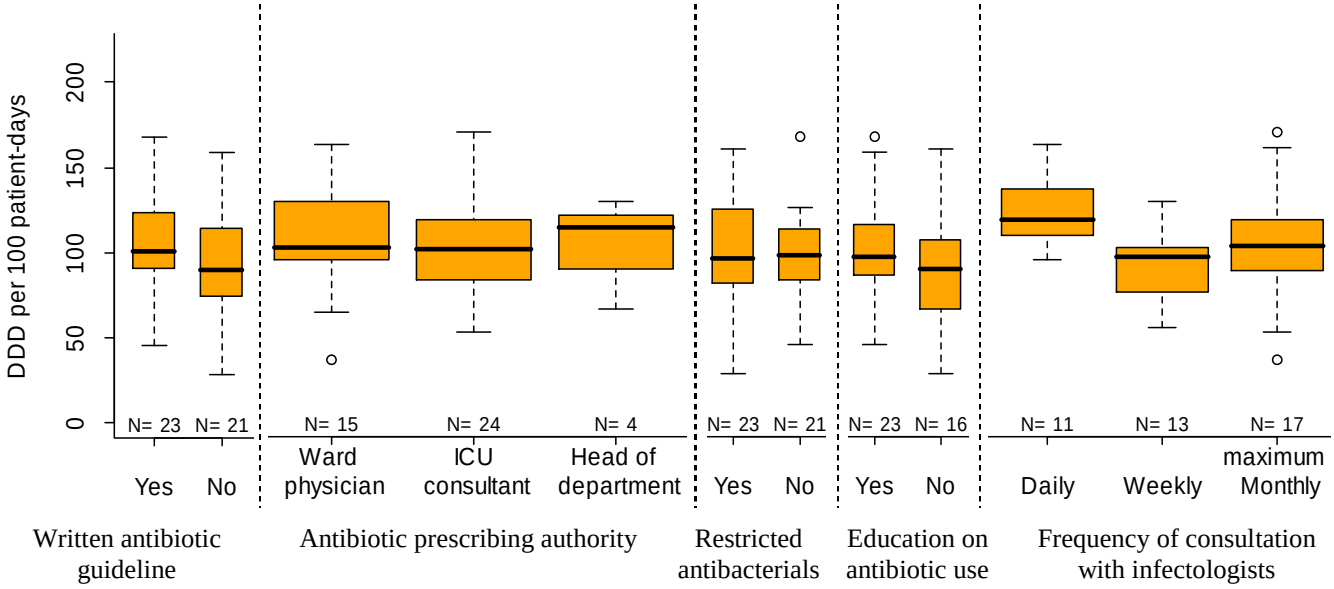
Table 6. Antibiotic consumption in DDD per 100 patient-days in Hungarian ICUs, 2006

	All ICUs			Medical	Interdisciplinary	Surgical
Antibacterial group	Mean±SD[a]	Min	Max	Mean		
J01 Systemic antibacterials	98.69 ±30.88	27.91	167.79	90.60	92.26	113.16
J01A Tetracyclines	0.77±1.91	0.00	8.75	0.94	0.90	0.45
J01CA Penicillins with extended spectrum	2.00±6.08	0.00	38.35	1.79	0.65	5.00
J01CE Beta-lactamase sensitive penicillins	0.59±1.39	0.00	6.65	0.13	0.71	0.70
J01CF Beta-lactamase resistant penicillins	0.35±1.16	0.00	5.44	0.00	0.11	1.17
J01CR Combinations of penicillins including beta-lactamase inhibitors	19.89±8.13	4.07	43.87	15.35	22.45	16.96
J01DB First-generation cephalosporins	0.31±0.63	0.00	2.32	0.00	0.24	0.55
J01DC Second-generation cephalosporins	5.33±7.98	0.00	39.16	3.57	3.16	11.30
J01DD Third-generation cephalosporins	15.19±9.44	0.00	40.22	10.24	15.88	15.45
J01DE Fourth-generation cephalosporins	1.28±1.86	0.00	7.46	1.03	0.90	1.86
J01DH Carbapenems	9.46±6.62	0.24	35.90	8.76	8.31	12.02
J01E Sulfonamides and trimethoprim	0.94±1.72	0.00	9.22	0.85	1.23	0.41
J01FA Macrolides	2.41±3.00	0.00	12.45	1.66	2.80	1.67
J01FF Lincosamides	2.57±2.19	0.00	9.58	3.22	2.22	2.39
J01G Aminoglycoside antibacterials	6.40±4.91	0.15	19.68	6.56	6.33	6.62
J01M Quinolone antibacterials	17.02±9.33	3.27	47.96	22.43	16.38	14.42
J01XA Glycopeptide antibacterials	5.57±10.32	0.00	64.42	3.63	3.13	12.35
J01XD Imidazole derivatives	8.49±8.38	0.00	44.16	10.45	6.73	9.61

[a]SD: standard deviation

The relationship between total antibacterial use in ICUs and the existence of different elements of antibiotic policy are summarized on Figure 15. In this pooled analysis, none of them showed to be accompanied by lower antibiotic use.

Figure 15. The existence of different elements of antibiotic policy and pooled antibacterial use in Hungarian ICUs.



Association between antibiotic use in ICUs and the length of stay (R=0.104, P=0.502) or the case-mix index (R=0.023, P=0.857) could not be detected in the correlation analysis.

Pharmacokinetic study

Twelve of the 14 enrolled patients completed the study (Table 7). One patient dropped out owing to development of severe renal failure and another patient was excluded because of transfer to another ICU before study completion. The primary diagnoses leading to ICU admission are listed in Table 8. A high severity of illness (according to the Simplified Acute Physiology Score II) [170], a low albumin level and a high estimated CL_{CR} were general characteristics of the patient population (Table 7).

Table 7. Patient characteristics and steady-state levofloxacin pharmacokinetic parameters following intravenous administration of 500 mg/day maintenance dose to critically ill patients with ventilator-associated pneumonia

Patient characteristics		Pharmacokinetic parameters	
Parameter	Value (mean ± SD)	Parameter	Value (mean ± SD)
Males/females	7/5	$fC_{max,ss}$ (mg/L)	8.13 ± 1.64
Age (years)	40.25 ± 22.01	$fC_{min,ss}$ (mg/L)	0.48 ± 0.33
Weight (kg)	72.33 ± 13.34	fV_d (L)	82.51 ± 18.93
SAPS II	40.42 ± 14.93	$T_{1/2\beta}$ (h)	6.23 ± 1.60
CL_{CR} (mL/min)	169.63 ± 55.94	CL (mL/min)	178.09 ± 57.98
Albumin (g/L)	29.08 ± 5.35	*f*AUC (mg·h/L)	49.63 ± 15.60

SD: standard deviation; SAPS II: Simplified Acute Physiology Score II, determined on the day of admission; CL_{CR}: estimated creatinine clearance based on the Cockroft–Gault formula; $fC_{max,ss}$: maximum free plasma concentration at steady state; $fC_{min,ss}$: minimum free plasma concentration at steady-state, fV_d: volume of distribution; $T_{1/2\beta}$: elimination half-life; CL: total body levofloxacin clearance; *f*AUC: steady-state area under the free plasma concentration−time curve over 24 h.

All patients received levofloxacin as monotherapy, with an average length of treatment of 7 days. Levofloxacin was well tolerated and no adverse effects were observed in any of the patients. Of the 12 patients with ventilator-associated pneumonia (VAP), 11 had a microbiologically confirmed bacteriological aetiology. A total of 14 levofloxacin-sensitive microorganisms were isolated (Table 8), with dual infection in three cases. Methicillin-sensitive *Staphylococcus aureus* and *Pseudomonas aeruginosa* sensitive to most antipseudomonal drugs were the most frequent isolates.

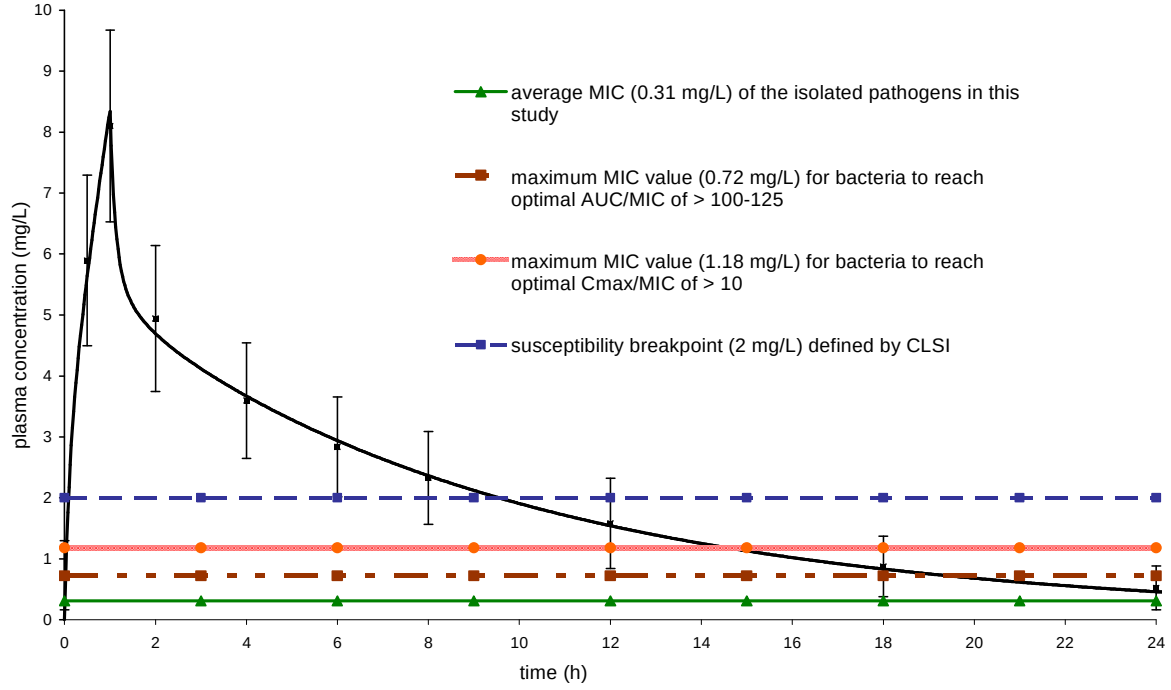
Table 8. Admission diagnosis, causative pathogens, individual pharmacokinetic and PK/PD parameters and outcome of levofloxacin therapy in critically ill patients with ventilator-associated pneumonia

Patient ID	Primary diagnoses	Aetiological agents	MIC (mg/L)	$fC_{max,ss}$ (mg/L)	$C_{max,ss}$ (mg/L)	*f*AUC (mg·h/L)	AUC (mg·h/L)	$C_{max,ss}$/MIC	AUC/MIC	Outcome	
										Clinical	Microbiological
01	SAH	N/A	N/A	7.68	11.13	41.26	59.80	N/A	N/A	Improved	N/A
02	T	*E. coli*	0.016	10.60	15.36	82.42	119.45	960.05	7465.67	Failure	Eradication
		E. cloacae	0.063					245.77	1911.21		Eradication
03	CSI	*K. pneumoniae*	0.125	5.94	8.61	34.87	50.53	68.90	404.26	Cure	Eradication
04	MT	*P. aeruginosa*	0.25	9.54	13.82	67.11	97.26	55.29	389.03	Cure	Eradication
05	MT	*S. aureus*	0.125	6.82	9.88	35.98	52.14	79.04	417.10	Improved	Eradication
		S. marcescens	0.125					79.04	417.10		Eradication
06	MT	*S. maltophilia*	0.25	6.31	9.15	28.28	40.98	36.60	163.93	Cure	Failure
07	BT	*P. mirabilis*	0.063	7.74	11.22	43.16	62.56	179.55	1000.88	Cure	Eradication
08	SAH	*S. aureus*	1	9.55	13.84	61.41	89.00	13.83	89.00	Improved	Failure
09	MT	*P. aeruginosa*	0.25	10.22	14.81	59.73	86.57	59.22	346.28	Cure	Eradication
10	MT	*S. aureus*	1	6.30	9.13	47.50	68.84	9.13	68.84	Cure	Eradication
		P. aeruginosa	0.125					73.06	550.75		Eradication
11	SAH	*E. coli*	0.032	7.62	11.04	41.12	59.59	345.11	1862.27	Cure	Eradication
12	MT	*Enterobacter* spp.	0.25	9.26	13.42	52.68	76.35	53.68	305.41	Cure	Eradication

MIC: minimum inhibitory concentration; $fC_{max,ss}$: maximum free plasma concentration at steady-state; $C_{max,ss}$: calculated maximum total plasma concentration at steady-state (i.e. after adjusting for 31% protein binding); *f*AUC: steady-state area under the free plasma concentration−time curve over 24 h; AUC: calculated steady-state area under the total plasma concentration−time curve over 24 h (i.e. after adjusting for 31% protein binding); SAH: subarachnoid haemorrhage; N/A: not available; T: trauma; CSI: cervical spine injury; MT: multiple trauma; BT: brain tumour

The mean steady-state levofloxacin plasma concentration–time profile is shown in Figure 16, whilst overall pharmacokinetic variables are summarised in Table 7.

Figure 16. Mean (±SD) steady-state plasma levofloxacin concentration − time profiles after multiple intravenous administration of 500 mg/day to patients with ventilator-associated pneumonia (n=12).



SD: standard deviation, CLSI: approved susceptibility breakpoint for levofloxacin established by the Clinical and Laboratory Standard Institute (CLSI) and applied for most pathogens; AUC: area under the total plasma concentration-time curve over 24 h, C_{max}: maximum total plasma concentration, MIC: minimum inhibitory concentration

The individual patient pharmacokinetic parameters, the MIC values for levofloxacin of the causative pathogens and the achieved PK/PD ratios are summarised in Table 8. The threshold AUC/MIC for a successful clinical/microbiological outcome of >100–125 was achieved in all but two cases. Optimal C_{max}/MIC (>10) was attained in 10 of the 11 cases with microbiologically confirmed bacteriological aetiology. Considering the average pharmacokinetic parameters; the highest levofloxacin MIC of bacteria that would fulfil the minimum AUC/MIC ratio (≥100) for the present dosage regimen is 0.72 mg/L. To achieve the optimal C_{max}/MIC (≥10), the present dosing regimen would allow an MIC of 1.18 (Figure 16). Table 9 shows the number of subjects (out of the 12 patients) with desired PK/PD target achievement at different dedicated MIC values with 500 mg or 1000 mg daily levofloxacin regimen.

Table 9. Number of subjects of the 12 critically ill patients with ventilator-associated pneumonia achieving desired pharmacokinetic/pharmacodynamic targets with 500 mg or 1000 mg daily levofloxacin, considering total drug exposure [a]

	Target PK/PD parameters	Study MIC [b]	Dedicated MIC values			
		0.31 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L [c]
500 mg/day levofloxacin	**C_{max}/MIC**	Number of patient achieving the marked C_{max}/MIC				
	10	12	12	12	8	0
	12	12	12	12	5	0
	AUC/MIC	Number of patient achieving the marked AUC/MIC				
	30	12	12	12	12	7
	50	12	12	12	11	1
	100	12	12	11	1	0
	125	12	12	7	0	0
	250	4	7	0	0	0
	Target PK/PD parameters	Study MIC [b]	Dedicated MIC values			
		0.31 mg/L	0.25 mg/L	0.5 mg/L	1 mg/L	2 mg/L [c]
1000 mg/day levofloxacin	**C_{max}/MIC**	Number of patient achieving the marked C_{max}/MIC				
	10	12	12	12	12	8
	12	12	12	12	12	5
	AUC/MIC	Number of patient achieving marked AUC/MIC				
	30	12	12	12	12	12
	50	12	12	12	12	11
	100	12	12	12	11	1
	125	12	12	12	7	0
	250	12	12	7	0	0

MIC: minimum inhibitory concentration; C_{max}: maximum total plasma concentration; AUC: area under the total plasma concentration–time curve; [a] desired pharmacokinetic/pharmacodynamic target achievement, calculated from the observed individual pharmacokinetic parameters after correction for 31% protein binding (i.e. *f*AUC/0.69 = AUC); [b] average MIC of the 14 pathogens isolated in this study; [c] approved susceptibility breakpoint for levofloxacin established by the Clinical and Laboratory Standard Institute (CLSI) and applied for most pathogens

At the end of levofloxacin therapy, eight patients were completely cured, three patients showed an improvement and treatment failed in one patient. Bacterial eradication of the aetiological agent was achieved in nine cases. However, in two cases merely a decrease in the number of colony forming units (CFU) was observed. No superinfection was observed in any of the cases.

We observed a weak positive association (R=0.73; P=0.005) between levofloxacin clearance (CL) and creatinine clearance ($CL_{CR)}$. Further relationship between pharmacokinetic parameters and patient parameters were not revealed.

6. DISCUSSION

6.1. *Drug utilisation studies*

6.1.1. National trends in antibacterial utilisation

Although some authors have suggested using more than one measurement unit for antibiotic consumption in hospitals [54,171], we showed in a previous study that hospital antibiotic consumption expressed in either DDD per 100 patient-days, DDD per 100 admissions, or DDD per 1,000 inhabitants and per day, were strongly associated both at national and regional level [172]. Therefore we used only one measurement unit, the WHO recommended DDD per 100 patient-days to present our results. However, as for practical purposes the European Surveillance of Antimicrobial Consumption (ESAC) project uses the DDD per 1,000 inhabitants and per day to express hospital antibacterial use, we also calculated our data in DDD per 1,000 inhabitants and per day to enable comparison with ESAC data.

The political change in 1989 proved to be a milestone in the Hungarian antibiotic utilisation. The antibiotic assortment widened in consequence of the drug import liberalisation, while the hospital antibiotic consumption decreased between 1990 and 1996 [3]. In our results standardized total hospital antibiotic consumption in Hungary between 1996 and 2007 remained relatively stable. Some of the changes in the pattern of use were gradually taken over from the 1990's: the decrease in the utilisation of the tetracyclines, the beta-lactamase-sensitive penicillins and the sulfonamide-trimethoprim group, which began after the political change in 1989 [3] continued until the end of our study period. The significant growth of fluoroquinolone consumption and of the penicillin and beta-lactamase inhibitor combinations has been unbroken since 1990.

Data from the ESAC have shown large inter-country variations in hospital antibiotic consumption and that consumption in Hungary was the third lowest in Europe when expressed as DDD per 1,000 inhabitants and per day in 2002 [160] and fourth lowest in 2005 [173]. Individual reports [174-182] show that antibiotic consumption in the Hungarian hospital care is even lower compared to other European countries when expressed in DDD per 100 patient-days. One characteristic of data on hospital care in Hungary is that it covers a large number of acute care and chronic care institutions and hospital beds accounting for a large number of admissions and of patient-days, larger than in other countries [183,184]. Based on data available from the Hungarian National Health Fund Administration database, approximately 30% of the patient-days included in this study originated from chronic care

institutions [161]. One explanation for the very low national hospital antibiotic consumption – expressed in DDD per 100 patient-days – could be the large number of patient-days and larger proportion of chronic care patient-days compared to other European countries.
On the basis of the proportional distribution of antibiotic use, Hungary was a frequent user of sulfonamides, macrolides and penicillins, and an average user of fluoroquinolones and tetracyclines compared to other European countries in 2002 [160]. According to the latest available data from the ESAC database (year 2005) [173], the share of macrolides, lincosamides and fluoroquinolones from the total hospital antibiotic use in Hungary were above the European average.

The proportional use within the penicillin group had some special features: the contribution of the penicillin and beta-lactamase inhibitor group (mainly co-amoxiclav) to the overall hospital penicillin use was substantial even on an international scale [160,173]. In 2005, within Europe, only Luxemburg had higher proportional penicillin and beta-lactamase inhibitor consumption within the penicillin group than Hungary (87% vs. 83 %) [173]. This could be explained in part by their broad spectrum of activity and consequent extended usage in empiric antibiotic therapy and the availability of low price generics. Beta-lactamase-sensitive (J01CE) and beta-lactamase-resistant (J01CF) penicillins (only oxacillin was available in Hungary) played only a marginal role, in contrast with other European countries where there was a considerable use (Norway, Sweden, Denmark, Finland) [160,173]. Oxacillin products have been discontinued to be on the market since the second half of 2003, and this practically annuled their use: in 2005 only 4 packages of oxacillin injection was used, while from 2006 zero.
When focusing only on hospital-specific antibiotics defined by the ESAC team (see section 4.4.1. on page 14), Hungary was average consumer both in absolute and in relative manner [160,173,173]. Glycopeptides were used at a lower extent compared to other European countries, probably because of the relative better Methicillin resistant *Staphylococcus aureus* (MRSA) situation in 2002 [11,160], but by 2005 its consumption became average [173]. Monobactams (i.e. aztreonam) have never been marketed in Hungary; hence their use could not be detected.

As concerns the share of different cephalosporin generations in Hungarian hospitals, the relative frequency of third-generation cephalosporin use was above the European average in 2005 (37% vs. 27%), whereas the relative use of the first-generation cephalosporins was well below it (6% vs. 20%). The relative use of second and fourth-generation cephalosporins was average [173].

Heterogeneous use of antibacterials is desirable to reduce the selection pressure for antibacterial resistance [185,186]. Unfortunately, as the number of active agents in the DU90% segment decreased, and the co-amoxiclav combinations highly dominated the antibacterial use, the national hospital antibacterial use became less diverse by 2007.

6.1.2. Regional differences in antibacterial utilisation and its determinants

Large interregional differences in total hospital antibiotic consumption were found during 1996-2007. In other countries like Germany or Norway significant regional variations in total hospital antibiotic consumption have not been found, however they used hospital level data [174,175]. In Hungary, the relative use of different antibiotic classes has also greatly varied across regions. Such regional variety in prescribing preferences for certain antibiotic classes has been reported in Germany [174], but not in Norway [175].

As I discussed earlier, the less heterogeneous the antibiotic use is, the more the chance for the selection of antibacterial resistance [185,186]. In 2007, the heterogeneity of antibiotic use were also deficient in some regions and parallel the use of some antibacterials (e.g. first-generation cephalosporins) was almost completely missing. In the multiple linear regression the number of reported infections had stronger predictive value compared to the case mix index. However the collective explanatory value of the two independent variables was still moderate, as could not explain 40 % of the regional differences.

Some authors have reported an association between hospital antibiotic consumption and special care areas, e.g. intensive care, onco-haematology, infectiology [174,181,187-189]. In this study, we found no association between hospital antibiotic consumption and the percentage of patient-days in intensive care or infectious disease units at regional level. The percentage of patient-days in onco-haematology units in each region could not be obtained.

We recently showed regional variations in antibiotic consumption in the Hungarian ambulatory care with a West-East gradient [190]. In the present study, we found quite similar geographical pattern for hospital antibiotic consumption, with a slightly larger difference between regions with the lowest and the highest antibiotic consumption. We found that

regional hospital antibiotic consumption was associated with regional antibiotic consumption in ambulatory care. In our previous study, interregional differences in antibiotic consumption in ambulatory care were associated with socio-economic determinants [190]. As data on the socio-economic status of admitted patients is not available, we could not investigate this variable as determinant of hospital antibiotic use. However as poor socio-economic status is often associated with poor health status [184], − which is incorporated in the case-mix index − socio-economic status may at least indirectly influence antibiotic use in hospitals.

The major limitation of this study was the lack of hospital level antibiotic consumption data. Due to confidentiality issues, at present, antibiotic consumption data from individual hospitals are not publicly available in Hungary. This means that we could not evaluate the effect of hospital size, hospital type or university affiliation, which explained some of the inter-hospital differences in antibiotic consumption in other studies [174,175,181]. However, the standardized distribution of different size and type of hospitals is quite even across Hungary. Additionally, regions with university centres did not show higher hospital consumption compared to other regions (see Figure 7). Due to unavailability of data, we were also not able to test associations between several other possible determinants for hospital antibiotic consumption (e.g. the number of surgical interventions, the number of infectiologists per 1,000 hospital beds, marketing activity, etc).

6.1.3. Antibiotic related activities in Hungarian adult ICUs and in their parent institute

Growing number of publications assign hospital/clinical pharmacist as a key member of antibiotic programs that aim to rationalise antibiotic use [191-196]. According to the consensus conference of the Antibiotic Resistance Prevention and Control (ARPAC) European project the existence of a drugs and therapeutics or antibiotic committees with the involvement of a pharmacist would be a minimum requirement [194]. Our results are concordant with the results of the ARPAC project where 146 (86%) of the participating hospitals reported the existence of drugs and therapeutics committee with 81% pharmacist involvement (in Hungary 58 (97%) of the ICUs parent institute have drugs and therapeutics committee with 86% pharmacist involvement) [197]. Separate antibiotic committees were present more frequently in the surveyed European hospitals (53% vs. 38 % in Hungary). Multidisciplinary committees were reported from 51 (30%) of European hospitals compared to 7 hospitals in our survey (12%) [197]. The meeting frequencies of these hospital committees were also comparable, most often quarterly meetings were held [197]. While

written guideline for empiric antibiotic therapy was available in 77% of the ARPAC hospitals and 21% of the ICUs in a Swedish study [198], Hungarian ICUs had this document in 45%. We also proved that the information content of these guidelines at Hungarian ICUs were incomplete and only half (13 guideline, 48%) of them were developed by the responsible hospital committees appointed by the ARPAC project.

Local education on antibiotic use and on the consequences of resistance development were performed in less than half of the Hungarian ICUs (26 ICU, 43%) contrast to 136 (80%) of European hospitals [199]. While the participation of hospital/clinical pharmacist in these educational sessions was rare both in European hospitals (34 hospitals, 20%) and in Hungarian ICUs (3 ICUs; 9%), the participation rate of pharmaceutical companies were undesirably high (53 European hospitals 31 % vs. 14 Hungarian ICUs, 40%).

The ARPAC consensus conference recommended the survey of standardized antibiotic use (expressed in DDD per 100 patient-days) minimum once a year and that the results should be fed back personally to the prescribers. As the member of the multidisciplinary team the pharmacist should be the responsible person [194]. However more than half of the Hungarian intensive care units analysed antibiotic use, mostly these surveys focused on financial aspects. Standardized antibiotic use was calculated only at five (8%) ICUs and pharmacist were involved in 3 out of the five cases. In contrast, in Sweden 26 out of 35 ICUs (76%) received report on antibiotic use at least once a year [198]. It should be noted that in 15 Hungarian ICUs the quality of antibiotic use (e.g. adherence to guidelines) were also assessed. Only one ICU reported that the prescribers received personal feed-back on the results of the antibiotic use survey. Pharmacists were rarely consulted in antibiotic related questions. One possible explanation is the lack of pharmacist presence in daily rounds. Only 28 European hospitals (16%) have pharmacist participating in daily rounds, while the presence of pharmacist in European ICUs is unknown [196]. The active participation of pharmacist in bed-side consultations could be achieved by specially trained ward pharmacists. The so called „antibiotic pharmacists" have been practising in the United States since many years, while among European countries pharmacist − specifically trained in antibiotic therapy − were educated and employed in the United Kingdom first [200]. Other European countries including Hungary are far away from this, but as stated in the ARPAC publication hospital/clinical pharmacist could have a bright future [194]. To be able to achieve this goal, first the claim for more active pharmacist participation should be established as presently the Hungarian physicians do not think that the involvement of pharmacists would rationalise antibiotic use.

Before concluding the results, it should be noted that the ARPAC project surveyed antibiotic policies and other related aspects of antibiotic use on hospital level, while our questions partly referred to hospitals, partly to ICUs. However, taking into account the special role of ICUs within hospitals as concerns antibiotic use, I think that our conclusions are relevant also in cases where we compared ICUs to European hospitals.

6.1.4. Antibiotic use in Hungarian adult intensive care units

This preliminary analysis on antibiotic use in Hungarian adult ICUs found that antibiotic consumption varied widely from 27.91 to 167.79 DDD per 100 patient-days. Substantial, from 3.5 up to 14 fold differences in the total antibiotic use in ICUs were also detected in a German [201] (45.0 –179.9 DDD per 100 patient-days); Swedish [66] (60.5 – 214.3 DDD per 100 patient-days) and in a pan European study [60] (34.8 – 499.2 DDD per 100 patient-days). The median consumption of 98.38 DDD per 100 patient-days and mean consumption of 102.11 DDD per 100 patient-days in this study are slightly lower than the figures reported from other European studies [60,61,201].

However like in a few Hungarian ICUs, relatively low mean antibiotic consumptions have been reported in Swiss ICUs by Loeffler [62] (46.2 and 68.3 DDD per 100 patient-days in the surgical and medical ICU, respectively). The relatively low antibiotic use in the Swiss ICUs was ascribed to the strong control efforts, to the close collaboration with the infectious diseases consulting service and to aggressive diagnostic practices. However, as concluded by the author, inappropriate antibiotic use might have still occurred in that unit [62].

However, the limitations of the DDD per 100 patient-days method to express antibiotic use should be borne in mind when comparisons are made.

In our results, the total systemic antibacterial use did not differ considerably in medical, interdisciplinary and surgical ICUs. This is in line with previous findings which found that total antibacterial use is not related to ICU type [56,58,59].

Swedish researchers found that antibiotic consumption was higher among ICU patients in tertiary care centres [69]. Similarly, de With et al. [59] concluded that when comparing the total use of antibiotics between ICU cohorts, data adjustment is required for ICU category (i.e. level of care). This finding has been confirmed in our study as tertiary care ICUs had significantly higher antibacterial use than ICUs located in regional or local hospitals. Other studies found no significant association between university status and the use of antibacterials

[58,201]. Researchers from Sweden [66,198] reported higher antibiotic use in ICUs as level of care increased, but it has not reached statistical significance.

Clinicians often justify high antibiotic use in their particular setting with differences in patients' morbidities. The case-mix index (CMI) is an easily available economic parameter calculated using diagnosis-related groups. Recently Kuster et al. [202] found significant correlation between antibiotic use and CMI across various specialities of a university hospital. We could not find association between CMI and antibiotic use at ICU level. An ICU study from Sweden also did not find association between a specific illness severity score (APACHE II: Acute Physiology and Chronic Health Evaluation II) and antibiotic use [198]. Such a relationship could have been concealed because differences in patient case-mix not reflected by patient severity scores. However, these results are in agreement with the notion that factors other than patient-related factors determine the use of antibiotics [203].

As the length of stay is related to the denominator of the formula used to calculate antibiotic use (DDD per 100 patient-days) its influencing role on total antibiotic use can be expected. It is claimed that higher patient turnover (i.e. high number of admissions with shorter length of stay (LOS) may result in higher antibiotic use when expressed as DDD per 100 patient-days [54,68]. In contrast, in the study of Walther et al. [198] significant positive correlation was found between antibiotic use at ICUs and average LOS. In our study, antibiotic use in Hungarian ICUs was irrespective of the length of stay.

In Hungarian ICUs the proportional use of oral agents ranged between 1.70 and 53.85 % of total antibacterial use. The relative use of oral and parenteral agents in ICUs are scarcely reported in the literature, only Loeffler et al. reported that oral agents made up 13% and 26% of total use in a Swiss surgical and medical ICU, respectively [62]. High consumption of oral antibacterials in some Hungarian ICUs may be a matter of concern because of bioavailability issues [204-208].

In general, the preferred antibiotic groups in Hungarian ICUs were penicillins with beta-lactamase inhibitors, quinolones and third-generation cephalosporins. Update from German ICUs [209] shows that the same antibiotic groups belong to the top three as in Hungary. In Sweden, cephalosporins (mainly cefuroxime) were the most frequently used class of antibiotics (26% of median consumption) followed by isoxazolyl penicillins and carbapenems [66,198], and this has been confirmed by a recent study [61].

As it was previously shown [59] stratification by ICU type is important when the consumptions of certain antibiotic classes are compared. In our study the use of second generation cephalosporins and glycopeptides were higher in surgical units. In German

surgical ICUs [58] the use of glycopeptides were also higher compared to other ICU types. Associations between ICU type and use of macrolides and lincosamides (higher use in medical ICUs) and imidazoles (higher use in surgical and interdisciplinary ICUs) were also observed in a previous German work [59]. In Hungarian ICUs the use of lincosamides but not macrolides was the highest in medical ICUs while the consumption of imidazoles was highest in medical and surgical ICUs.

Different strategies of antibiotic policy like guideline implementations, education of physicians, restrictions measures, involvement of infectious disease specialist, etc. have been shown to decrease the antimicrobial use [57,64,65,187,210-212].

In our study neither elements of antibiotic policy showed lower aggregated antibiotic use in those ICUs where they were present. Several factors can explain this finding. First, observations before and after the intervention may need to show its effects on antibiotic use [192,213]. Secondly, often several strategies are combined in the interventions [57,65,214,215], while in our study the different approaches to control antimicrobial use were rarely present simultaneously (e.g. written antibiotic policy and antibacterial restrictions were present in only 13 ICUs).

6.2. *Pharmacokinetic study*

This study assessed the pharmacokinetics of levofloxacin based on free drug level measurements as well as the efficacy of levofloxacin monotherapy in critically ill patients with ventilator-associated pneumonia (VAP) who had normal renal function. Further theoretical considerations were also applied to the average pharmacokinetic data to predict below which MIC values the present dosing regimen would be effective. As only free drug is active and the unbound state is a prerequisite for tissue distribution [216,217], one strength of our study is the measurement of free drug levels. According to a recent paper, it is recommended that all pharmacokinetic/pharmacodynamic (PK/PD) indices should be referenced to the unbound (free) fraction of the drug [111]. As only free drug is the active moiety and the MIC is measured in plasma protein-free medium [216-219] these recommendations appear to be justifiable. In contrast, the optimal PK/PD values appointed by clinical studies, which were also used as target values in this dissertation, were determined by using total serum concentrations [127,129,140]. To compare our results with other studies and with target PK/PD values that are based on total drug levels, despite its pitfalls [125] we were forced to make adjustments for protein binding.

The pharmacokinetic parameters in this study are in line with the data of Rebuck et al [148]. With a 500 mg daily regimen they obtained an AUC value of 66.1 ± 15.7 mg·h/L (mean ± standard deviation) compared with our 71.92 ± 22.62 mg·h/L adjusted value (i.e. 49.63/0.69, considering 31% protein binding). Other studies conducted on ICU patients are in contrast with our findings, as AUC values of 110 ± 56.48 mg·h/L [151] and 151 mg·h/L (range 137–174 mg·h/L) [149] were reported with the same levofloxacin regimen. The large discrepancy compared with the study of Boselli et al. [149] might be explained by the differences in renal function of the patients (mean CL_{CR} of 63 mL/min [149] vs. 169 mL/min in this study), and age-related changes in renal function are presumed to be at least partly responsible for these pharmacokinetic differences (mean age 71 years vs. 40 years). Pharmacokinetic results from our study also differ from the findings of Pea et al. [144] as they achieved similar AUC values ($AUC = 2 \times AUC_{0–12}$ = 67.8 ± 20.82 mg·h/L) with a doubled maintenance dose (2 × 500 mg/day). All these findings might be partially related to different analytical and methodological procedures and to well known interindividual pharmacokinetic variability frequently observed in critically ill patients.

In the present study the mean steady-state plasma concentrations were constantly above the average MIC of the clinical isolates. The individual PK/PD parameters exceeded both thresholds of clinical/microbiological efficacy (C_{max}/MIC > 10 and AUC/MIC > 100–125) in all but one case. As clinical success (improvement or cure) was attained in all but one case and bacterial eradication was achieved in 9 of the 11 assessable cases, our data support these PK/PD considerations. With regard to the high survival rate in this study, it should be noted that we excluded severe patients with septic shock and those with an estimated CL_{CR} < 50 mL/min, which limits the generalisation of our results to other critically ill populations. Also, the high PK/PD indices observed in our study with 500 mg/day levofloxacin treatment may not always be achieved owing to differences in the susceptibility patterns (MIC distributions) of pathogens at individual institutions. Typically, pathogens with marginal susceptibility are staphylococci and pneumococci and the non-fermenters such as *Pseudomonas* spp. Special attention should be paid to establish the MIC values of these pathogens.

As in various ICU studies differences were found in AUC levels, optimal PK/PD indices could be ensured up to different MIC values (0.66 mg/L [148], 1.10 mg/L [151] and 1.5 mg/L [149] with a 500 mg/day regimen and 0.68 mg/L with a 2 × 500 mg daily regimen [144] vs. 0.72 mg/L in this study). All of these MIC threshold values are lower than the most widely

used susceptibility breakpoint (2 mg/L) established by the Clinical and Laboratory Standard Institute (CLSI) [169].

Considerations based on PK/PD indices predict that for optimal antibacterial therapy against bacteria with an MIC of 2 mg/L, a minimum $C_{max,ss}$ of 20 mg/L and a minimum AUC of 200–250 mg·h/L are required, i.e. approximately three-fold higher for the optimum AUC than is achievable with the present dosing regimen in critically ill patients with normal renal function. As at the highest dose (1000 mg/day) that could be safely administered [221] only bacteria with an MIC of ≤1.5 mg/L predicted to be treated successfully, there is a potential risk of levofloxacin therapy failure in cases when the bacterium is labelled as being sensitive (MIC ≤ 2 mg/L) in the microbiology report [144,153,222]. Thus, lowering the susceptibility breakpoint for levofloxacin is proposed. As a lower clinical MIC breakpoint for levofloxacin (i.e. 1 mg/L) has already been defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [223] and has already been decreased for *Staphylococcus aureus* by CLSI (i.e. from 2 mg/L to 1 mg/L in 2005), the acceptance and widespread application of this value should be considered.

In the multiple linear regression analysis the dose-related pharmacokinetic parameters (C_{max}, AUC) that determine therapy outcome did not show relationship with the tested patient parameters therefore they cannot be predicted from them. These are in line with the findings of Spanish researchers who found no association between AUC and patient parameters and found very weak relationship between the C_{max} and SAPS II scores or the body weight [151].

7. SUMMARY

In this thesis I set out to provide insights into national and regional hospital antibacterial use in Hungary. I also intended to assess the antibiotic related activities of Hungarian intensive care units (ICUs) and their parent hospitals and quantify the antibiotic use in ICUs. Finally, I aimed to determine the pharmacokinetic/pharmacodynamic (PK/PD) parameters and appropriateness of levofloxacin therapy in a special patient group.

My main findings are as follows:

- Total hospital antibiotic consumption in Hungary expressed as defined daily dose (DDD) per 100 patient-days remained relatively stable between 1996 and 2007 and some of the observed changes in the pattern of consumption are consistent with the national and international recommendations (e.g. decreased use of tetracyclines, increased use of respiratory fluoroquinolones). However, the low first-generation cephalosporin and narrow spectrum penicillin (beta-lactamase-sensitive and beta-lactamase-resistant penicillins) use as well as the less diverse antibacterial use require attention. The reason for substantial share of macrolide, lincosamide, fluoroquinolone, third-generation cephalosporin and penicillin plus beta-lactamase inhibitor consumption from total hospital antibacterial use should also be addressed in future pharmacoepidemiologic studies.
- There were constantly large interregional differences in the Hungarian hospital antibacterial consumption. The pattern and heterogeneity of antibacterial use also differed considerable between Hungarian regions. The differences in total hospital antibacterial use were moderately explained by the number of reported infections and the case mix index (CMI), and surprisingly we observed a positive relationship between the regional hospital care and ambulatory care antibiotic consumption. All of these may suggest that other determinants that could not be explored in this dissertation (e.g. regional prescribing habits or marketing practices) may also contribute to regional differences. Therefore future studies should aim at collecting data for each individual hospital, as well as data on other possible determinants for hospital antibiotic consumption.
- Minimal requirements defined by the Antibiotic Resistance Prevention and Control (ARPAC) project have not been fulfilled in many aspects: multidisciplinary hospital

committees were not realized, and the activity of these committees in antibiotic guideline development was not satisfactory. The information content of empiric antibiotic guidelines was also deficient. Continuous education and calculation of standardized antibiotic use was rare in Hungarian ICUs. The role of pharmacist remained marginal in every field. All these findings suggest the need for appointment of a responsible, multidisciplinary antibiotic management team including a pharmacist.

- Consumption of systemic antibacterials varied widely (up to six fold) and the proportional use of oral agents also greatly differed in Hungarian adult intensive care units (ICUs). It was difficult to explain these differences; the only factor which showed significant association with total antibacterial use was the ICU category (i.e. level of care). However in many Hungarian ICUs this was the first time when antibacterial use was expressed in a standardized consumption unit. The striking differences in total antibiotic use and high use of oral agents in some ICUs – that could not be explained satisfactory in this study – may indicate room for improvement.
- Low dose (500 mg per day maintenance dose) intravenous levofloxacin proved to be an effective regimen in this limited number of critically ill patients with ventilator-associated pneumonia (VAP) and predicted to be effective when the minimum inhibitory concentration (MIC) of the pathogen is below 0.72 mg/L. The target pharmacokinetic/pharmacodynamic (PK/PD) thresholds of clinical/microbiological efficacy were exceeded in almost every case. The lack of relationship between C_{max}, AUC and patient parameters do not allow any prediction for these pharmacokinetic parameters. According to the measured pharmacokinetic parameters, the highest safe levofloxacin maintenance dose (1 g/day) would ensure optimal PK/PD levels up to a MIC of 1.5 mg/L, which is lower than the currently used MIC susceptibility breakpoints for levofloxacin, therefore lowering of MIC susceptibility breakpoints for levofloxacin should be considered.

In conclusion, the continuous and close monitoring of antibacterial use at national, regional and local level should be considered as an important public-health priority to find problematic areas and trends which may require interventions. Also, the determination of optimal dosage in specific patient populations (i.e. ICU patients) could help in ensuring clinical/microbiological efficacy.

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9. ACKNOWLEDGEMENTS

First of all, I wish to express my sincere gratitude to my supervisor **Dr. Gyöngyvér Soós** for her support and guidance of my work. I am thankful for her criticism, encouragement and numerous advices during my Ph.D. work.

I am indebted to **Prof**. **Dominique Monnet** for introducing me to drug utilisation studies and to **Prof**. **Elisabeth Nagy** for providing the possibility and strong support to work in close collaboration with the **Institute of Clinical Microbiology**.

Special thanks to **Dr. Mária Matuz** and **Dr. Edit Hajdú**, my closest colleagues, co-authors, and friends for their numberless help and support.

I express my thanks to all my co-authors for their collaboration and help in this work: **Prof. Lajos Bogár, Dr. Péter Doró, Dr. János Gardi, Dr. Ágnes Hegedűs, Dr. Anna Molnár, Dr. Zoltán Pető and Dr. Réka Viola.**

Thanks are also due the **staff of the Intensive Care Unit** at the New Clinic and to the **staff of the Endocrinology Laboratory** for their technical assistance and for the friendly work-atmosphere.

I am grateful the **IMS PharmMIS Consulting Company** for providing me invaluable data on antibiotic consumption.

I am deeply grateful to **my family** for their continuous support and encouragement that I have received during these years.

10. ANNEX

10.1. *Definitions of pharmacokinetic and pharmacodynamic parameters*

Pharmacokinetic parameters (in alphabetic order)

AUC [111]: The area under the serum/plasma concentration–time curve at steady-state over 24 h unless otherwise stated. Dimensions: Concentration-time (e.g. mg·h/L or mg·h/mL).

Clearance (CL) [112]: The volume of serum or blood completely cleared of the drug per unit time. Dimensions: Volume per time (e.g. ml/min).

Elimination half-life: ($T_{1/2\beta}$) [112]: The time that it takes for serum concentrations to decrease by half in the elimination phase. Dimension: Time (e.g. h).

Peak or C_{max} (level, concentration) [111]: the highest concentration reached or estimated in the compartment of reference (in this thesis: serum/plasma). Dimensions: Concentration (e.g. mg/L or mg/mL).

Though or C_{min} (level, concentration) [111]: the lowest concentration reached or estimated in the compartment of reference (in this thesis: serum/plasma). Dimensions: Concentration (e.g. mg/L or mg/mL).

Volume of distribution (V_d) [112]: A hypothetical volume that relates drug serum concentration to the amount of drug in the body. Dimension: Volume (e.g. L or ml)

The prefix "*f* " refers to the free fraction of the drug, e.g. *f*AUC indicating that it is the free, unbound fraction of the drug that is meant or used. The subscript "ss" refers to the pharmacokinetic steady state condition, e.g. *f*Cmax,ss is maximum free serum/plasma concentration of the drug estimated or reached under steady-state conditions.

Pharmacodynamic parameters (in alphabetic order)

In vivo post-antibiotic effect (PAE) [111]: The difference in time for the number of bacteria in a tissue of treated animals versus controls to increase 1 log10 over values when drug concentrations in serum or the infection site fall below the MIC. The in vivo PAE thus includes the effects of sub-MIC concentrations. Dimensions: Time (e.g. h).

Minimum inhibitory concentration (MIC) [113]: The lowest concentration of antibiotic sufficient to inhibit bacterial growth when tested in vitro. Dimensions: Concentration (e.g. mg/L or mg/mL).

Minimum inhibitory concentration 90 (MIC90) [113]: The lowest concentration of antibiotic required to inhibit the growth of 90% of tested isolates. Dimensions: Concentration (e.g. mg/L or mg/mL).

10.2.*Ethical approval of the pharmacokinetic study*

Szegedi Tudományegyetem
Szent-Györgyi Albert Orvos- és Gyógyszerésztudományi Centrum

Human Investigation Review Board
University of Szeged
Albert Szent-Györgyi Medical and Pharmaceutical Centre

H-6701 Szeged
P.O.Box: 427
Hungary

1691

The Human Investigation Review Board on its last meeting discussed the ethical relations of the research proposal to be carried out at the Department of

Dr. Pető Zoltán egyetemi tanársegéd, Szegedi Tudományegyetem Általános Orvostudományi Kar, AITI Új Klinikai Részleg (6725 Szeged, Semmelweis u. 6.)

The title of the proposed project is:

Szérum antibiotikum szint mérése, és ennek jelentősége nozokomiális pneumonia, illetve szeptikus állapot esetén intenzív osztályon fekvő betegek esetében.

The scheme of the experiments complies with the ethics of research. It agrees with the declaration of the Medical Word Federation proclaimed in Helsinki in 1964, therefore, the Human Investigation Review Board does not raise any objection to it from ethical point of view and supports it.

Szeged, 2003. 08. 05.

Dr. Wittmann Tibor
President of the
Human Investigation Review Board
University of Szeged
Hungary

10.3. *Publications related to the thesis*

I. **R Benko**, M Matuz, P Doro, E Hajdu, G Nagy, E Nagy, Gy Soos: [Antibiotic consumption between 1996 and 2003: national survey and international comparison]. *Orv Hetil* 2006; 147(26): 1215-1222.

II. **R Benko**, M Matuz, P Doro, R Viola, E Hajdu, DL Monnet, G Soos. Hungarian Hospital Antibiotic Consumption at the regional level, 1996-2005. *Infection*. 2009;37(2):133-137.

III. **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* [under publication]

IV. **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.

V. **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.