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Antibiotic Use Optimization Program in the Largest Croatian University Hospital – Benefits of Restrictions on Unlimited Antibiotic Use

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A B S T R A C T

The aim of this study was to obtain the relevant information on antibiotic use in a 750-bed Croatian university hospital. The study has been designed as a 2-point prevalence interventional analysis. For each patient on antibiotic therapy, diagnosis, indication for treatment, antibiotic therapy, dosage and route of administration together with the results of microbiological studies (if available) were obtained. After the first prevalence analysis in 2001, a restriction on unlimited antibiotic use was introduced. The second analysis, performed in 2002, after restrictions on antibiotic use, revealed reductions in the rates of restricted release antibiotics and overall antibiotic use with decreases from 38.6% to 36.9% and 23.4% to 23.2% respectively (p=0.87). The first survey showed that the 5 most often prescribed antibiotics in the therapy of bacterial infections were: gentamicin, other aminoglycosides, carbapenems, amoxycillin+clavulanate and vancomycin with proportions of 14.8%, 10.3%, 8.2%, 7% and 7% respectively. In the year 2002, the most prescribed antimicrobial drugs in the therapy of bacterial infections were: gentamicin, quinolones, vancomycin, carbapenems and cefuroxime with proportions of 18.6%, 11.4%, 9.7%, 9.3% and 8% respectively. A reduction in the proportions of doubtful antibiotic therapy, from 24.6% before the intervention, to 24.2% after the restrictions, accompanied by a 0.4% rise in the rates of indicated antibiotic therapy was also observed (p=0.93). Our study shows that restrictions on formerly unlimited use of antimicrobials, even when leading to an improvement in their prescribing, do not necessarily cause rapid and significant reduction in the overall use of antibiotics or explicit positive financial effects.

Key words*: antibiotic, antimicrobial therapy, antimicrobials, treatment, optimization, reduction, hospital*

Introduction

Control of the infectious diseases by vaccination, antibiotics and public health measures is surely one of the greatest achievements of modern medicine. Under the pressure of evolutionary adaptation however, many microorganisms became resistant to antibiotics to which they have been formerly susceptible. Rising microbial resistance in turn spawned the development of many new, expensive, broad spectrum antibiotics that were widely available, readily accepted and usually overzealously or indiscriminately used by the physicians, contributing in that way further to the rising rates of antimicrobial resistance and increase in health care costs. In response, many experts and organizations have called for increased efforts to limit the overuse of antimicrobial agents both in community and hospital settings[1–4].

The aim of this study was to obtain the relevant information on antimicrobial use in the largest university affiliated hospital in Croatia. Among other things, special attention was given to: overall use of antibiotics per department, indications for use, source of infections and utilization of microbiological studies. We used a point-prevalence interventional method.

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Materials and Methods

Setting

University Hospital Rebro is a *750*-bed tertiary care facility in Zagreb, Croatia. The hospital has undergraduate and postgraduate teaching courses including training programmes for residents in internal medicine, pediatrics, neurology, psychiatry, ophthalmology, urology, oncology, several surgery subspecialties, neurosurgery, nuclear medicine and clinical pharmacology.

Unit of Clinical Pharmacology provides supervision and dose monitoring for patients on restricted release antimicrobial agents. Clinical pharmacology counseling on appropriate dosing, possible interactions and allergic reactions is available to all hospital wards. Bulletins containing information on drugs, antimicrobial dosing and cost, recommendations for empiric therapy and microbial resistance patterns in the hospital are distributed monthly to all physicians.

Study design

This study had been designed as a 2-point prevalence interventional analysis (interrupted time series design – ITS). All hospitalized patients have been surveyed for antibiotic treatment, once a year for two consecutive years. For each patient on antibiotic therapy, diagnosis, indication for treatment or prophylaxis, antibiotic treatment, dosage and route of administration together with the results of microbiological studies (if available) were obtained. Members of the unit of Clinical Pharmacology performed data collection and registration.

After the first point prevalence analysis in 2001, a restriction on unlimited antibiotic prescribing was introduced, consisting of mandatory written forms that were required by the central pharmacy for every parenterally prescribed antibiotic and an obligatory written request for every restricted release antibiotic, authorized only after consultation with clinical pharmacologist, microbiologist or an ICU attending physician. Within 48 hours of the start of therapy, it was determined whether antibiotic therapy was necessary. A point system for indicated antibiotic therapy was introduced in order to serve as guidelines to physicians for the improvement of antibiotic prescribing (Table 1). The second point prevalence analysis was performed in 2002.

The annual antibiotic costs were calculated in US dollars for both periods, based on the prices of antimicrobial agents provided by the hospital pharmacy.

Data analysis

Statistical analysis was performed using STATISTICA version 6.1 software. Where appropriate, data were

TABLE 1
POINT SYSTEM FOR INDICATED ANTIBIOTIC THERAPY

Sign / Laboratory value	Points
Positive blood culture	3
Positive microbiological studies	2
Body temperature > 37.5 °C	1
L >10x10^9	1
L >10x10^9 + neseg. L	2
CRP >10	1
Clinical signs of infection	1
Other laboratory or RTG signs of infection	1

Points <3 doubtful indication for antibiotic therapy,
3 or >3 necessary antibiotic therapy

TABLE 2
ANTIBIOTICS USAGE COMPARISON – UNIVERSITY HOSPITAL REBRO

Department	2001.			2002.		
	No. Beds	Patients on antibiotics	%	No. Beds	Patients on antibiotics	%
Physiatric	14	0	0.0	14	0	0.0
Internal medicine	145	55	37.9	138	48	34.78
Cardiosurgery	25	7	28.0	22	11	50.0
Surgery	116	35	30.2	117	40	34.19
Cardiology	59	6	10.2	60	5	8.33
Neurosurgery	42	7	16.7	49	12	24.49
Neurology	115	16	13.9	114	12	10.53
Nuclear medicine	12	0	0.0	11	0	0.0
Ophthalmology	76	27	35.5	68	22	32.35
Oncology	78	13	16.6	64	8	12.5
Pediatrics	110	33	30.0	112	35	31.25
Psychiatry	84	0	0.0	78	1	1.28
Urology	52	17	32.7	44	13	29.55
University Hospital Rebro	928	216	23.4	891	207	23.2

analyzed using chi-square tests. The Wilcoxon signed rank test was used to compare pre- and post-interventional points awarded for indicated antibiotic therapy. The costs of antimicrobial therapies were based on concurrent wholesale drug prices in Croatia. The hospital's review board approved the protocol of this study.

Results

The point prevalences of antibiotic use for the whole hospital in 2001 and 2002 were 23.4% and 23.2% respectively. In the 2001, the highest prevalences of antibiotic treatment were observed in the Departments of Internal medicine, Ophthalmology, Urology, Surgery and Pediatrics with 37.9%, 35.5%, 32.7%, 30.2% and 30% respectively. A year later, highest rates of antibiotic therapy were noted in the Departments of Cardio-surgery, Internal medicine, Surgery, Ophthalmology and Pediatrics with 50%, 34.78%, 34.19%, 32.35% and 31.25% respectively (Table 2).

The first survey showed that the 5 most often prescribed antibiotics in the therapy of bacterial infections were: gentamicin, other aminoglycosides, carbapenems, amoxycillin+clavulanate and vancomycin with proportions of 14.8%, 10.3%, 8.2%, 7% and 7% respectively. The following year, the most prescribed antimicrobial drugs were: gentamicin, quinolones, vancomycin, carbapenems and cefuroxime with proportions of 18.6%, 11.4%, 9.7%, 9.3% and 8% respectively (Table 3).

Out of all prescribed antimicrobial drugs in the first analysis, 61.4% were first line, while 38.6% were restricted release antibiotics. The second survey showed a decrease in the rates of restricted release antibiotics to 36.9% (p=0.87), see Table 4.

TABLE 4
PROPORTION OF RESTRICTED RELEASE ANTIBIOTICS AND DOUBTFUL ANTIBIOTIC USE IN THE THERAPY OF BACTERIAL INFECTIONS

Antibiotic	2001		2002	
	N	%	N	%
First line	87	61.4	94	63.1
Restricted release	53	38.6	55	36.9
Total	140	100	149	100
Indicated	104	75.4	113	75.8
Doubtful	34	24.6	36	24.2
Total	138*	100	149	100

* Two formularies were excluded from analysis due to the fact that they were inappropriately filled in

It is worth noting that we observed a reduction in the proportions of doubtful antibiotic therapy, from 24.6% before the intervention, to 24.2% after the introduction of prescription restrictions, accompanied by a 0.4% rise in the rates of indicated antibiotic therapy (p=0.93). Moreover, overall reduction of antibiotic costs between the compared periods amounted to 445 251 $ in savings.

The commonest conditions requiring antibiotic treatment in the first study were: urinary tract infections, sepsis, pneumonia, fever and respiratory tract infections with prevalence of 24.3%, 10.7%, 10%, 9.3% and 6.4% respectively. The following year, diagnoses that most often lead to antibiotic use were: urinary tract infections, fever, pneumonia, sepsis and other conditions with prevalence of 26.8%, 12.8%, 11.4%, 8.7% and 11% respectively (Table 5).

In addition, all departments of the hospital, with the exception of Urology and Surgery, showed a significant increase in the mean number of points allocated for indi-

TABLE 3
PROPORTIONS OF THE 10 MOST OFTEN PRESCRIBED ANTIBIOTICS FOR THE THERAPY OF BACTERIAL INFECTIONS

2001				2002			
Antibiotic	N	No PDD	%	Antibiotic	N	No PDD	%
Gentamicin	1	36	14.8	Gentamicin	1	44	18.6
Aminoglycosides (amikacin, netilmicin)	2	25	10.3	Quinolones	2	27	11.4
Carbapenems (imipenem, meropenem)	3	20	8.2	Vancomycin	3	23	9.7
Amoxycillin+clavulanate	4	17	7.0	Carbapenems (imipenem, meropenem)	4	22	9.3
Vancomycin	5	17	7.0	Cefuroxime	5	19	8.0
III generation cephalosporins (ceftazidime, ceftriakson)	6	16	6.6	Metronidazole	6	19	8.0
Cefuroxime	7	16	6.6	III generation cephalosporins (ceftazidime, ceftriakson)	7	15	6.3
Cloxacillin	8	15	6.2	Amoxycillin+clavulanate	8	11	4.6
Quinolones	9	14	5.8	Cloxacillin	9	11	4.6
Metronidazole	10	13	5.3	Cefepime	10	10	4.2

No PDD – number of prescribed daily doses

TABLE 5
COMPARISON OF THE COMMONEST CONDITIONS REQUIRING ANTIBIOTIC TREATMENT

Diagnosis	2001			Diagnosis	2002		
	N	No	%		N	No	%
UTI	1	34	24.3	UTI	1	40	26.8
Sepsis	2	15	10.7	Fever	2	19	12.8
Pneumonia	3	14	10.0	Pneumonia	3	17	11.4
Fever	4	13	9.3	Sepsis	4	13	8.7
RTI	5	9	6.4	Other	5	11	7.4

UTI – urinary tract infection, RTI – respiratory tract infection

TABLE 6
DEPARTMENTS WITH CORRESPONDING MEAN POINT NUMBERS FOR INDICATED ANTIBIOTIC THERAPY

Department	2001	2002
	Number of mean points	Number of mean points
Pediatrics*	4.2	5.8
Urology	4.0	3.6
Internal medicine*	3.7	5.0
Neurosurgery*	3.7	6.0
Oncology*	3.6	4.9
Cardiosurgery*	3.3	5.8
Neurology*	3.3	4.8
Cardiology*	3.0	6.0
Surgery	3.0	3.2
Ophthalmology†	–	0.8
Physiatric department†	–	2.0
University Hospital Rebro*	3.53	5.01

* Wilcoxon signed rank test $p<0.05$, † departments that have not supplied data for 2001 were excluded from analysis

cated antibiotic therapy (Table 6), according to the point system for antibiotic therapy that had been introduced together with the limitations on antibiotic use (Table 1).

Discussion

The goal of our antibiotic policy is to ensure the correct and rational use of antimicrobial drugs. Having experienced rising drug costs, coupled with increasing microbial drug resistance, fund limits imposed by a national health system undergoing a reform and struggling economy of a postwar, transitional country, hospital's team for drug monitoring decided to assess the present antibiotic policy by conducting a point prevalence study.

It showed a prevalence of antibiotic use of 23.4%, which is in comparison with the results of other prevalence studies (25% to 60%) somewhat lower[5–9]. However, it highlighted a high prevalence of restricted release antibiotics (38.6%), with carbapenems and vancomycin being among the top five most prescribed antimicrobial drugs.

The second analysis, performed after the introduction of restrictions on antibiotic use, divulged reductions in the rates of restricted release antibiotics and overall antibiotic use with decreases from 38.6% to 36.9% and 23.4% to 23.2% respectively. It also demonstrated an improvement in antibiotic prescribing throughout the hospital. Even though statistically insignificant, the decrease in antibiotic use could have, at least partially, accounted for the saving of 445 251 $, representing a 15% of the annual hospital budget for antimicrobial agents. Although we are unaware of any other concurrent changes in practice that could have preferentially affected antibiotic use during our research, confounding variables such as: random fluctuations, seasonal effects or secular trends (e.g. decrease in price of antimicrobials during the intervention) cannot be excluded.

The scoring method for indicated antibiotic use (Table 1) has been devised in collaboration with the colleagues at the University Hospital Rijeka (Croatia) and the Karolinska Institutet (Sweden)[10]. It has generally been well accepted by the clinicians of our hospital, although the highest acceptance rates could be observed among the residents. The mandatory written formularies required by the central pharmacy for parenteral and restricted release antibiotics contain this scoring system, thus serving as a helpful tool for residents in coping with the differences in antimicrobial prescribing patterns between various departments.

The randomized controlled trial (RCT) is seen as the criterion standard methodology for the evaluation of health care interventions[11]. However, there are many instances where it is impossible or impractical to use RCTs. In an interrupted time series (ITS) design, data are collected over time before and after an intervention is introduced to detect whether the intervention has an effect significantly greater than the underlying secular trend. The greatest threat to validity of an ITS study is that an event other than the control of the researchers occurred at the same time as the intervention, thereby making casual inferences impossible[12]. A recent analysis has demonstrated that this threat could not be ruled out explicitly in 66% of the performed ITS studies[13].

Further studies are required to clarify why physicians overzealously prescribe antibiotics to hospitalized patients[14]. Patients' demands for antimicrobials are often cited as a reason for unnecessary prescriptions in the outpatient setting[15]. Possible reasons proposed for excessive antibiotic use in hospitals include acutely ill and complex status of patients, diagnostic uncertainty, pressure to keep lengths of stay short, and prescribing by clinically inexperienced physicians as in teaching hospitals[16]. Physicians may also have a low threshold to give antimicrobials, because they believe that these agents are unlikely to cause harm, and in the same time ignore the possible consequences not only for the individual patient but also for the broader microbiological environment[14].

There are few publications assessing the effect of guidelines on antibiotic utilization. The best method(s) to improve use is still not known[17]. Multidisciplinary approach, continuity of the process and the roles of clinical pharmacologists, microbiologists and infectious disease specialists are usually stressed[4–6,18–25].

Our study shows that restrictions on formerly unlimited use of antimicrobials, even when leading to an improvement in their prescribing, do not necessarily cause rapid and significant reduction in the overall use of antibiotics or explicit positive financial effects.

Take home messages:

- Rising rates of antimicrobial resistance and increase in health care costs are the primary reasons for increased efforts to limit the overuse of antimicrobial agents both in community and hospital settings.
- Possible reasons for excessive antibiotic use in hospitals include acutely ill and complex status of patients, diagnostic uncertainty, pressure to keep lengths of stay short, and prescribing by clinically inexperienced physicians as in teaching hospitals.
- The best method(s) to improve antibiotic use is still not known.
- Many authorities emphasize multidisciplinary approach, continuity of the process of antimicrobial use control and the roles of clinical pharmacologists, microbiologists and infectious disease specialists.

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PROGRAM OPTIMIZACIJE UPOTREBE ANTIMIKROBNIH LIJEKOVA U NAJVEĆOJ HRVATSKOJ SVEUČILIŠNOJ BOLNICI: KORISTI OD RESTRIKCIJA NA NEOGRANIČENU UPOTREBU ANTIMIKROBNIH LIJEKOVA

S A Ž E T A K

Svrha ovog istraživanja bila je sakupiti relevantne informacije o upotrebi antimikrobnih lijekova u hrvatskoj sveučilišnoj bolnici sa 750 kreveta. Istraživanje je dizajnirano kao intervencijska analiza s 2 točke prevalencije. Za svakog bolesnika na antimikrobnoj terapiji sakupljeni su podaci o antimikrobnoj terapiji, dijagnozi, indikaciji za terapiju, dozi i putu primjene lijeka zajedno s rezultatima mikrobiološke obrade (ukoliko su bili dostupni). Nakon analize prve točke prevalencije u 2001 godini, uvedena je restrikcija na neograničeno propisivanje antimikrobnih lijekova. Druga analiza, provedena 2002, nakon uvedenog ograničenja na antimikrobne lijekove, pokazuje smanjenje postotka upotrebe antimikrobnih lijekova s ograničenim propisivanjem s 38.6% na 36.9% te smanjenje upotrebe svih antimikrobnih lijekova s 23.4% na 23.2% ($p=0.87$). U prvom istraživanju pet najpropisivanijih antimikrobnih lijekova u terapiji bakterijskih infekcija su bili: gentamicin (14.8%), drugi aminoglikozidi (10.3%), karbapenemi (8.2%), amoksicilin s klavulanskom kiselinom (7%) i vankomicin (7%). U 2002 godini, najpropisivaniji lijekovi u terapiji bakterijskih infekcija bili su: gentamicin (18.6%), kinoloni (11.4%), vankomicin (9.7%), karbapenemi (9.3%) i cefuroksim (8%). Također je zabilježeno smanjenje postotka upitne antimikrobne terapije, s 24.6% prije intervencije, na 24.2% nakon restrikcija, uz 0.4% porast udjela indicirane antimikrobne terapije ($p=0.93$). Naše istraživanje pokazuje da restrikcije na prethodno neograničenu upotrebu antimikrobnih lijekova, čak i kada dovode do poboljšanja u njihovu propisivanju, ne uzrokuju nužno brzo i značajno smanjenje ukupne potrošnje antimikrobnih lijekova ili jasno pozitivne financijske učinke.