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ORIGINAL PAPERS: CLINICAL OR BASIC RESEARCH

Efficacy of an Antibiotic Control Program in monitoring the consumption of Glycopeptides and Carbapenems in several surgical departments and the Intensive Care Unit of a Teaching Emergency County Hospital

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ABSTRACT

Objectives: *To evaluate the effect of an Antibiotic Control Program (ACP) on the consumption of Glycopeptides (GP) and Carbapenems (CP) in the Intensive Care Unit (ICU) and surgical departments of our hospital over three years, from 2003 to 2005 The program has become operational since January 2004.*

Method: *Our retrospective study estimated the Defined Daily Dose /100 bed days (DDD/100 BD) for GP and CP using the data provided by the hospital pharmacy statistics. We correlated antibiotic consumption with the length of stay (of hospitalization), mortality and cost savings. The quality of the antibiotic prescription was evaluated by the infectious diseases specialist. Ten departments with a total of 398 beds were compared over three years (2003, 2004, and 2005): an ICU (20 beds) and nine surgical departments (378 beds).*

Results: *The GP consumption increased by 30% in 2004, compared to 2003 (from 3.3 DDD/100 BD to 4.3 DDD/100 BD), but only by 4.6% in 2005, compared to 2004 (from 4.3 DDD/100 BD to 4.5 DDD/100 BD), in the ICU, while in the surgical departments it decreased by 50% in 2004, compared to 2003 (from 0.4 DDD/100 BD to 0.2 DDD/100 BD), and remained stable in 2005 (0.2 DDD/100 BD). The CP consumption was 2.5 DDD/100 BD during the first two years and increased by 12% in 2005, compared to 2004 (from 2.5 DDD/100 BD to 2.8 DDD/100 BD) in the ICU, while its value was 0.1 for each of the follow-up years in the surgical departments. The length of hospital stay was shorter in 2005 (6.58 days) and 2004 (6.67), compared to 2003 (6.94 days). The mortality rate in the surgical departments was higher in 2005 (2.28%) and 2004 (2.12%), compared to 2003 (1.44%), because the ICU has been formally included in other hospital departments since 2004. The proportion of antibiotic treatment costs within total hospital drugs expenditure decreased from 32.7% in 2003 to 20.3% in 2004, and 27% in 2005, respectively. Total cost savings of 553 904 Euro (2 046 634 Ron) were reported. None of these changes had any statistical significance ($p>0.05$). The number of escalation antibiotherapy courses in 2004 (19 courses) was higher than in 2003 (15 courses), $p=0.0018$. The number of unnecessary treatments decreased from 16 courses in 2004 to 9 courses in 2005 ($p=0.029$).*

Conclusion: *Despite the 50% reduction of GP consumption in the surgical departments during the first year of follow-up, the ACP failed to significantly decrease the consumption of GP and CP, the length of stay and the mortality rate in the ICU and nine surgical departments during the first two years of the follow-up. The program seemed to improve the quality of antibiotic prescription.*

Key words*: antibiotic control programs, antibiotic consumption*

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INTRODUCTION

Antimicrobial resistance is an increasingly widespread process in hospital settings all over the world. Multidrug resistant bacteria, both gram positive cocci and gram negative bacilli, are reported as key determinants of nosocomial infections. Frequent use of broad spectrum antibiotics, prolonged exposure to some antimicrobials (such as Vancomycin), suboptimal drugs concentrations, all combined with poor hand hygiene and a longer length of hospitalization, are risk factors and a selective pressure for the emergence of nosocomial antibiotic-resistant microbial strains (1-5).

Several strategies including prescribers education, formulary restriction, prior approval, streamlining, antibiotic cycling and computer-assisted programs have been proposed to improve antibiotic use (6). Infection prevention (e.g. by immunization) or the use of rapid diagnostic tests to reduce antibiotics administration should also be considered (7).

Antibiotic control programs have been recommended by the World Health Organisation since 2001 as a strategy for closely monitoring the process of microbial multidrug resistance, by limiting general access to new antibiotics. Each of these programs has two components:

a) an infectious disease (ID) physician – the key specialist of antibiotic control programs (particularly those developed in multidisciplinary university hospitals) (8), mainly involved in: coordinating local guidelines on antimicrobial treatment, which are further promoted by continuing education programs (9); approving the antimicrobial prescription of selected drugs (subsequently to patients' examinations) (10); and making a time evaluation of both antibiotic use and quality of treatment (11,12).

b) a computer-based or handwritten order form for selected antimicrobials; studies show that computer order forms are efficient and well accepted, also enabling dramatic changes in the prescribing behaviour (13).

Restricting antibiotics administration has been especially effective in reducing costs and excess of empiric use of broad spectrum drugs. In one large study of the effect of prior authorization for selected drugs, a 32% decrease in expenditure for parenteral antibiotics was accompanied by increased susceptibility of bacterial isolates to beta-lactam and quinolone antibiotics. There were no adverse effects on clinical outcome as measured by time to receive of appropriate antibiotics, survival, and discharge from hospital for patients with bacteremia caused by gram-negative bacilli (14).

In October 2003, an infectious diseases specialist joined the medical team of the Teaching Emergency County Hospital Brasov (a multidisciplinary setting with 1261 beds) and an Antibiotic Control Program (ACP) was introduced based on the the New York Presbyterian Hospital ACP provided by Prof. Richard B. Roberts (Weill Cornell Medical Center, USA).

According to the new program, all restricted antibiotics (Table 1) could be released by the hospital pharmacy only on the basis of a handwritten Order Form filled by physicians. An advice from the ID specialist is needed within 24 hours after the start of treatment (15). When none of the above mentioned regulations is met, the pharmacist has to immediately stop giving the medication. Even if an ID physician's expertise is mandatory, the final therapeutic decision is entirely the responsibility of the physician in the concerned specialty – the ID specialist having just an advisory role. The physician's Antibiotic Order Form (Table 2), should clearly state clinic diagnosis, the culture's

Ceftazidim (excepting ICU, Hematology, Burns unit, Dyalise, Oncology.)
Cefoperazon/Sulbactam
Cefepim
Cefpirom
Ticarcillin-Clavulanat (excepting ICU)
Amikacin (excepting ICU, Hematology, Burns unit,
Dyalise, Oncology)
Levofloxacin (iv)
Claritromicin (iv)
Imipenem – Cilastatin
Meropenem
Vancomycin
Teicoplanin
Linezolid
Fluconazol (iv)
Voriconazol
Caspofungin
Acyclovir (iv)
Antiretrovirals: Indinavir, Nelfinavir,
Zidovudine/Lamivudine

TABLE 1. PCA – Antibiotics under restriction

Patient name: _____

Record number: _____

Department: _____

Physician name: _____

Clinical diagnosis: _____

Bacteriologic diagnosis: _____

Previous antibiotic treatments: _____

Required antibiotic: _____

Valid arguments for required antibiotic: _____

Total dose: _____

Estimated duration of treatment: _____

Total cost of antibiotics: _____

TABLE 2. Antibiotic order form

results, reports on prior use of antimicrobials, reasons for prescribing an antibiotic with restricted use, the dosage and duration of treatment (12). ❑

METHOD

We carried out a retrospective study to assess hospital prescription of antibiotics after the introduction of the ACP. We selected two broad spectrum antibiotic classes used for multiresistant bacteria – Glycopeptides (GP) and Carbapenems (CP) – and ten important departments with high nosocomial infection risks – an ICU (20 beds) and nine surgeries (378 beds). As prolonged exposure to Vancomycin, the presence of intravascular devices and prior infection with methicillin resistant *Staphylococcus aureus* (MRSA) are well known risk factors for vancomycin intermediate-resistant *Staphylococcus aureus* (VISA) acquired infection (16,17,18), we believed it was important to determine the pattern of glycopeptides consumption in the departments with highest rates of severe sepsis and surgical site infections.

Since the comparison of antibiotic consumption between hospitals, different departments of the same hospital, or during a fixed period of time cannot be quantitatively expressed in grams or packages of the respective antimicrobial drug, we have calculated the number of Defined Daily Doses (DDDs) for each antibiotic and department (for a specific drug, the DDD corresponds to the assumed average maintenance daily dose for its main indication for an adult weighing 70 kg). The DDDs are assigned by WHO Collaborating Centre for Drug Statistics Methodology (Oslo, Norway) and updated every year (11,17). In Europe, the ARPAC (Antibiotic Resistance Prevention and Control) group recommends the number of Defined Daily Doses/100 bed days (DDDs/100 BD) as the unit of measurement of antibiotics consumption (www.abdn.ac.uk/arpac)

DDD/100 BD was calculated on the basis of amount (grams) of each antibiotic used by every concerned department (data were supplied by the hospital pharmacy statistics), number of beds, occupancy index and number of days (during the follow-up period).

We made a retrospective assessment of the prescription patterns of the two antibiotic classes and checked for the use of any systematic de-escalating approach. We compared the list of antibiotics received by individual patients with the examination notes of the ID physician. No bacteriological data were available at that moment due to technical problems.

We compared the reports of 2003 (that might be simply considered a reference year as the ACP was only implemented during its last three months) with those of 2004 and 2005, respectively.

The statistic analysis was performed by a *t student's test*, $p < 0.05$ being considered significant. ❑

RESULTS

The GP consumption in the ICU increased by 30% in 2004, compared to the previous year (from 3.3 DDD/100 BD, in 2003, to 4.3 DDD/100 BD, in 2004) but only by 4.6% in 2005, compared to 2004 (from 4.3 DDD/100 BD to 4.5 DDD/100 BD, respectively); in the surgical departments it fell by 50% in 2004, compared to 2003 (from 0.4 DDD/100 BD to 0.2 DDD/100 BD) while remaining stable during 2005 (0.2 DDD/100 BD) (Figure 1 and Table 3).

The CP consumption was 2.5 DDD/100 BD during the first two years and increased by 12% in 2005, compared to 2004 (from 2.5 DDD/100 BD to 2.8 DDD/100 BD), in the ICU, but it had a stable value of 0.1 DDD/100 BD during the whole follow-up period, in the surgical departments (Figure 2).

Differences in GP or CP consumption between the three years were not significant, either in the ICU or in surgeries ($p>0.05$). As expected, we found a significant difference between the GP and CP use in the ICU and the surgical departments ($p <0.001$).

No essential changes were observed in the surgery departments, concerning either length of stay (6.94 days in 2003, 6.67 days in 2004, and 6.58 days in 2005; $p>0.05$) or the mortality rate (1.44% in 2003; 2.12% in 2004; 2.28% in 2005; $p>0.05$). The ICU had a very high mortality rate in 2003 (83.76%) but since it was not considered an individual department at the beginning of 2004, we lacked indicators

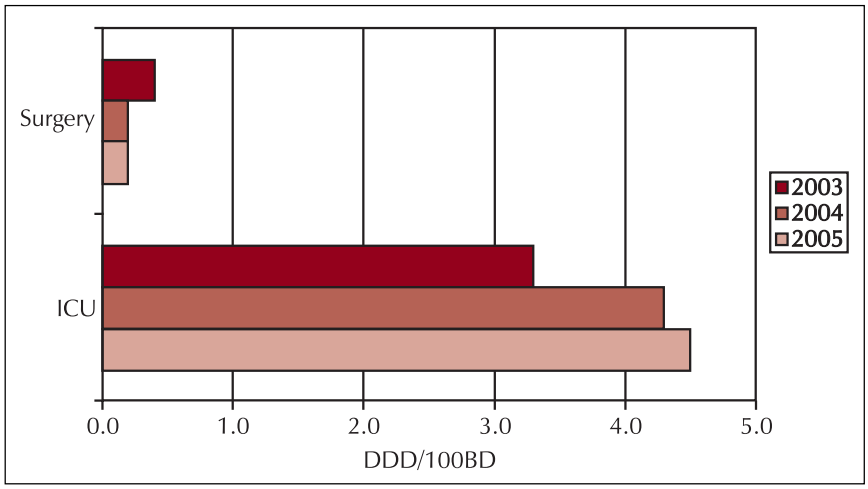

FIGURE 1. Glycopeptides (GP) Consumption in I.C.U. and Surgical Departments

			2003	2004	2005	P
ICU	GP	Teicoplanin	1.60	3.13	4.23	p>0.05
		Vancomycine	1.74	1.12	0.26	p>0.05
	CP	Imipenem/Cilastatin	2.03	2.38	1.97	p>0.05
		Meropenem	0.49	0.12	0.87	p>0.05
Surgery	GP	Teicoplanin	0.05	0.05	0.18	p>0.05
		Vancomycine	0.36	0.14	0.06	p>0.05
	CP	Imipenem/Cilastatin	0.04	0.05	0.08	p>0.05
		Meropenem	0.01	0.01	0.05	p>0.05

TABLE 3. Comparison of Glycopeptides and Carbapenems numbers of DDD/100 BD for 2003-2005

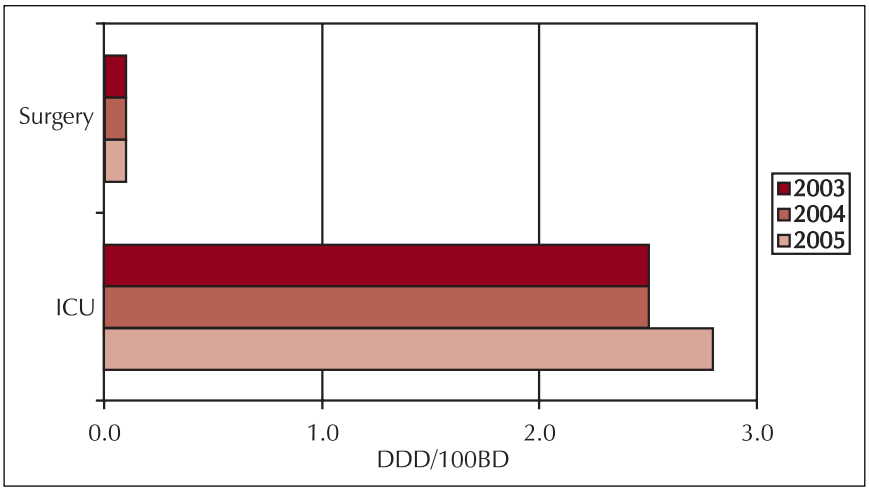

FIGURE 2. Carbapenems (CP) Consumption in I.C.U. and Surgical Departments

to compare the three follow-up years. The high mortality rate specific to ICUs is included in surgeries mortality rates reported during 2004-2005.

The costs of antibiotic treatments for inpatients (regardless of the medical department or the antibiotic class) accounted for 32.7% of the total drug expenses in 2003, 20.3% in 2004, and 27.% in 2005, respectively (Figure 3). A total cost savings of 553 904 euro (2 046 634 Ron) was succeeded during the three follow-up years.

We evaluated a total number of 142 antimicrobial therapy courses in 2003, 117 in 2004 and 103 in 2005, respectively, on the basis of the GP and CP prescribing patterns. We assessed for unnecessary treatments and de-escalation or escalation antibiotherapy (Table 4 summarises the criteria set by the ID specialist). Two significant differences, both in the surgery departments, were noticed:

1. An escalating antibiotic therapy for GP plus CP in 2004 (the first year when the ACP became operational) compared to the year 2003 (from 19 courses to 15 courses; p=0.0018);
2. A decrease of unnecessary treatments with GP and CP in 2005, compared to 2004 (from 16 courses to 9 courses; p=0.029).

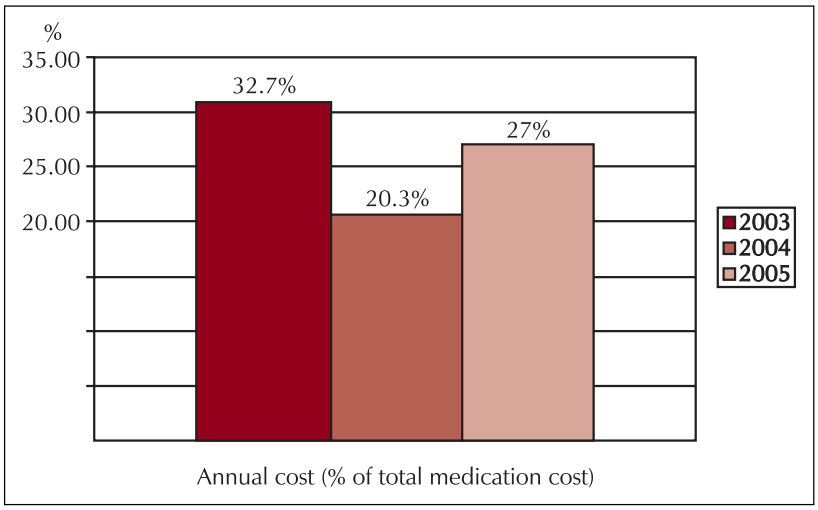

FIGURE 3. Antibiotic treatment expenses out of the total medication expenses

	2003		2004		2005		p
Medical Departments	ICU	Surgery	ICU	Surgery	ICU	Surgery	
No of unnecessary treatments*	19	22	24	16	15	9	p=0.029
No of de-escalation courses**	5	12	5	4	7	6	p>0.05
No of escalation courses***	16	15	19	19	16	21	p=0.018
Total number of GP and CP courses	51	91	70	47	51	52	

TABLE 4. Evaluation of antibiotic treatments

*We defined as unnecessary treatments the short course (1-2 days) GP/CP therapies, preceded and followed by other 1-2 courses with different antibiotics ("suspended treatment")

**De-escalation was considered the first line empiric treatment with GP/CP, followed by the use of a narow spectrum antibiotic within 1-3 days.

***Escalation defines the introduction of GP/CP medication after either a long period or at least two previous courses with other antimicrobials.

There was no difference in terms of de-escalating therapy between the follow-up years within the ICU and the surgical departments. ❑

DISCUSSIONS

The managerial intervention of introducing an antibiotic control program (ACP) developed under the key surveillance of an infectious disease specialist is usually successful (11,19). Most studies evaluate the complex impact of an ACP: shorter length of stay, lower mortality rates (20), lower antimicrobial costs (21), and effectiveness on bacterial resistance (20,21,22) and nosocomial infections.

The results of our study failed to show a significant reduction in GP and CP prescription rates, albeit surgery departments reported a 50% decrease of the GP consumption during the first year of the ACP intervention (compared to the year before the intervention). A detailed calculation of the DDD/100 BD for every surgical department might result in changes of the outcomes significance.

ACP did not yield a decrease of the CP consumption in any of the selected departments (which increased by 12% in the ICU during the first year of program development), maybe due to physicians' overall mistrust in the bacteriological diagnosis of Gram negative bacterial infections. Another reason for this might be the impossibility of ensuring a thorough control (by the hospital pharmacy) of the permanent stock of restricted antibiotics of the ICU (needed for empiric antibiotherapy administered to patients with severe sepsis within the first 1-2 hours after admission) (ID specialist's expertise was required by the ICU in only 14% of the total number of cases consulted in 2004). We may feel somehow reassured by the fact that similar hospital departments faced even greater difficulties in other countries. Lo et al (23), for instance, reported a lower percent of ID physician's consultations in a surgical ICU (5%), and other similar programs failed to significantly reduce the consumption of vancomycin (22). No variations in mortality from sepsis were detected in our hospital (probably being underreported) during the three follow-up years (according to DRG codes), reflecting complete independence from antibiotic restrictions.

Pharmacy expenditures for all antimicrobials, including antiviral, antifungal and antibacterial agents, decreased by 12.4% (from 32.7% to 20.3%) in the first year of the ACP development and by 5.7% (from 32.7% to 27%) in the second year of intervention. Antimicrobial cost savings in our study were very low compared with those from other reports: 19.4% (24) or 24.7% (20), in which they were the result of a careful selection of single agents within the relevant therapeutic class, as such an approach may have a dramatic impact on contract pricing (20).

The significant increase of escalating courses in surgeries during the first year of the ACP development was probably due to physicians' resistance to implementing the ID specialist's approval of antibiotherapy, albeit it was mandatory too (the administrative approval) before the start of this intervention. There were no changes in the escalating therapy in surgeries during the second year of the ACP development, but we found a decrease in the number of unnecessary GP and CP treatments. It might be possible to obtain more relevant results by designing a larger team to assess the quality of

antibiotherapy (it is likely that the ID specialist had not an objective judgement and the opinion of a single physician is not statistically sufficient).

We aim to further evaluate the efficacy of the three years ACP in internal medicine departments as well as in terms of direct communication and adherence to an ACP or acceptance of the Antibiotic Order Form. Calculating the DDD/100 BD for all the antibiotics used in the hospital could reveal other effects of ACPs. We also need to evaluate bacteriologic outcomes and nosocomial infections. ❑

CONCLUSION

Despite the 50% decrease of GP consumption in the surgical departments during the first year of the ACP development, there were no significant changes of the DDD/100 BD either for GP or CP in the ICU and surgeries.

No essential changes were observed concerning either the length of hospital stay or the mortality rate. The total cost savings were 553 904 Euro.

Further assessments of other important issues of antibiotic control programs are needed to conclude whether they are efficient or not in our multidisciplinary hospital.

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