Original Research

Antibiotic prescription and cost patterns in a general intensive care unit

Norberto KRIVOY, Wissam Abed EL-AHAL, Yaron BAR-LAVIE, Salim HADDAD.

ABSTRACT*

Antibiotic prescription habits, cost pattern, and the prospective intervention in an Intensive Care Unit were analyzed.

Methods: Data on antibiotic utilization and costs were collected prospectively from individual electronic charts from August 2003 to January 2004, and retrospectively from August to December 2002.

Results: A total of 180 and 107 patients were surveyed in 2002 and 2003. In 2002, Piperacillin-Tazobactam (13.8%) and Imipenem/Cilastin (11.2%) were the most prescribed medications; while, in 2003, Vancomycin (12.6%) and Imipenem/Cilastin (11.3%) were prescribed, respectively. Total defined daily dose (DDD) and Drug Utilization 90% (DU90%) index for 2002 and 2003 were 2031.15 and 2325.90 DDDs (p>0.1) and 1777.57 and 2079.61 DU90%, respectively (p>0.1). The Median Total Cost /100 admission days (CI 95%) were NIS13,310 (11,110;18,420) and NIS13,860 (6,710;18,020) (p=0.66), respectively.

Conclusions: Interventional programs should focus on promoting infectious control with rational antibiotic prescription aimed at minimizing the future emergence of bacterial resistance and futile expenses.

Keywords: Anti-Bacterial Agents. Drug Utilization. Hospitals. Israel.

RESUMEN

Se analizaron los hábitos de prescripción de antibióticos, el modelo de costes, y las intervenciones prospectivas en una Unidad de Cuidados Intensivos.

Métodos: Se recogieron prospectivamente datos sobre utilización y costes de antibióticos de los registros electrónicos individuales desde agosto de 2003 a enero de 2004, y retrospectivamente hasta diciembre 2002.

Resultados: Se investigó un total de 180 y 107 pacientes en 2002 y 2003. En 2002, la Piperacilina-Tazobactam (13,8%) y el Imipenem/Cilastina (11,2%) fue los más prescritos, mientras que en 2003, se prescribieron vancomicina (12,%) e Imipenem/Cilastina (11,3%). Las dosis diarias definidas (DDD) totales y el índice utilización90% (DU90%) para 2002 y 2003 fueron 2031,15 y 2325,90 DDD (p>0,1). La mediana de coste total /100 días de internamiento (IC95%) fue 13.310NIS (11.110;18.420) y 13.860NIS (6.710;18.020) (p=0,66), respectivamente.

Conclusiones: Los programas de intervención deberían enfocarse en promover el control de las infecciones con una prescripción racional de antibióticos centrada en minimizar las futuras apariciones de resistencia bacteriana y los gastos inútiles.

Palabras clave: Antibacterianos. Utilización de medicamentos. Hospitales. Israel.

(English)

INTRODUCTION

Antibiotics are the most frequently prescribed drugs among hospitalized patients especially in intensive care and surgical department. Programs designed to encourage appropriate antibiotic prescriptions in health institutions are an important element in quality of care, infection control and cost containment.[1-4]

Several authors[5-7] have reported concern about the continuous indiscriminate and excessive use of antimicrobial agents that promote the emergence of antibiotic-resistant organisms. Monitoring of antimicrobial use and knowledge of prescription habits are some of the strategies recommended to

* **Norberto KRIVOY**. MD. Division of Medicine, Clinical Pharmacology Unit. Rambam Medical Center and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology. Haifa (Israel).
Wissam Abed EL-AHAL. MSc (Pharm), Division of Medicine, Clinical Pharmacology Unit. Rambam Medical Center and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology. Haifa (Israel).
Yaron BAR-LAVIE. MD. General Intensive Care Unit. Rambam Medical Center and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology. Haifa (Israel).
Salim HADDAD. PhD. Pharmacy Service. Rambam Medical Center and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology. Haifa (Israel).

contain resistance to antimicrobials in hospitalized patients. Antimicrobial resistance substantially raises already-rising health care costs and increases patient morbidity and mortality.

The ICARE study established the high incidence of antibiotic resistance in an intensive care unit in comparison to the community.[8] It was demonstrated in the ICARE study that an infectious disease specialist intervention brought about a 45% decrease in antibiotic expenses.

A globally accepted 'dose standard unit' is important for drug utilization (DU) studies, particularly if the investigations are performed in different geographic areas and are to be compared. Health policy-makers obtained information based on bulk cost data and/or prescription volume of antibiotics, but these elements seemed not to offer any advantage over the defined daily dose (DDD).[9] The DDD is a technical unit for comparison - "the average recommended daily dose of a drug when used for its main indication".[9,10] The DDD methodology was developed in response to the necessity to convert and harmonize readily available volume data (bulk costs and prescriptions) from supply statistics of pharmacy inventory data into medically meaningful units, and to make crude estimates of the number of persons exposed to a particular drug or class of drugs.[9]

Drug utilization studies are particularly interesting if focused on the most frequently used groups of therapeutic drugs, such as antibiotics, chemotherapy, or those that constitute important therapeutic innovations. Drug utilization has been defined as "the prescribing, dispensing and ingesting of drugs".[11] The Drug Utilization 90% (DU90%) index was introduced as a simple, inexpensive and flexible method for assessing the quality of drug prescriptions. It identifies the drugs accounting for 90% of the volume of prescribed drugs after ranking the drugs used by volume of DDD.[12] The remaining 10% may contain specific drugs used for rare conditions in patients with a history of drug intolerance or adverse effects, complex co-morbid conditions and/or therapy prescribed by others.[13]

The Swedish Medical Quality Council has recommended the DU90% method for assessing general quality in drug prescribing.[14] The DU90% has been established as a reliable cut-off level for pharmacoepidemiology and economic surveys, and can be considered for the elaboration of a "health cost index".[9]

Drug utilization research (DUR) concepts and methods (DDD and DU90% index) can be used to study antibiotic use in different hospital admission units. The use of antibiotics is one of the main components in the direct cost of integral therapy, especially in a department of general intensive care.

The aim of this descriptive study was to analyze prospectively and retrospectively the antibiotic prescription habits, cost patterns, and the intervention effect of an Infectious Disease Specialist in a general intensive care unit situated in a university hospital.

METHODS

General information and Definitions

Rambam Health Care Campus is a 900-bed urban tertiary care teaching hospital affiliated with the B. Rappaport Faculty of Medicine of the Technion, Israel Institute of Technology, located in Haifa, Israel. The hospital has all major services, including medical and surgical subspecialities. The institution covers a population of 1,500,000 inhabitants and has 60,000 patients / admissions / year.

Prospective and retrospective data collection regarding drugs used , severity of the disease and patient outcome was performed in the General Intensive Care Unit, a 12-bed closed unit. Patients were admitted on a daily basis from the Emergency Department, operating rooms and other admission units (e. g Surgery, Medicine, Orthopedics).

Antibiotic prescription from the hospital formulary included those kept in ward-based stocks were performed directly by the physician to the nurse in charge. Non-formulary or "restricted" antimicrobial medications were ordered from the pharmacy using computerized registration forms for each patient and need to be authorized personally or by telephone by the on-call Infectious Diseases Specialist. A senior Infectious Diseases Specialist was always present during the morning (9 am) and/or evening (2 pm) Resident Rounds in the prospective study period only, while this facility was unavailable during the retrospective period.

The same observer (WA, a MSc pharmacy student) was responsible for recording and feeding the data into the computer programs. On admission, the following data were recorded on individual forms: admission date, age, gender, admission diagnosis, antibiotic name, delivery route, starting day, and therapy ending day. The dates of delivery of blood, urine, and other biological fluid cultures to the laboratory, culture results and antibiograms were recorded. Follow-up was performed on a daily basis.

Data collection was performed every day except for week-ends and holidays; the generated data from those days was recorded retrospectively on the first next working day. The individual clinical information, laboratory including bacteriological cultures, and prescription data was obtained from the web-centralized computer system Prometeus® (Rambam Medical Center Computer Systems, Haifa, Israel). The mean time bacteriology laboratory response in feeding biological fluid culture results into the system was 3.3 days.

The ATC-DDD classification for each drug was obtained from the WHO Guidelines.[10] Antimicrobial costs were obtained from the hospital pharmacy and the computer center. Costs are presented in New Israel Shekels (NIS) (NIS 1= US$ 0.23).

The DU 90% applied in this study consisted of the following steps:[12,15]

1) Identify all drugs that have an assigned DDD
2) Calculate the number of drugs that account for 90% of the total volume of DDDs

(=DU90%). As units of measurement (number of drugs and individual cost) are relative, the DU90% prescribing profile and Drug Cost 90% (DC90%) profiles were assumed to give a relevant picture of the prescription pattern.[13]

For the Center of Disease Control, appropriate antibiotic prescribing is defined as prescribing antibiotics only when they are likely to be beneficial to the patient, selecting agents that will target the likely pathogens and using these agents at the correct dose and for the proper duration".[16]

Exposure to an antibiotic was considered to be at least one dose of a prescribed antibiotic given during the survey. Antibiotic course was considered when a patient received 7 or more of days of therapy. An 'incomplete course' was when a patient received less than 7 days of therapy.

The data obtained in both study periods was fed into an Excel program prepared especially for the survey and the Prizm 3.0 Graph-Pad program for further analysis. Data analysis was performed accordingly, using contingence tables, non-parametric analysis and one-way analysis of the variance. A value of $p<0.05$ was considered as significant.

Prospective and Retrospective Data Collection

Data on individual antibiotic prescription, utilization patterns and antibiotic costs were collected prospectively daily from hospitalized patient charts from August 27, 2003, up to January 31, 2004, and retrospectively August 27, 2002, up to December 31, 2002, in patients for whom at least one antimicrobial medication was prescribed by the attending or resident physician and delivered by a nurse. Blood and other biological fluids culture results were also obtained systematically from the same computerized system.

Table 1. General information

	2002	2003	Δ%	p value**
Number of patients in survey	180	107	-40.6	ns
Male	135	76		
Female	45	31		
Total admission days	1381	1863	7.8	0.12
"Therapeutic window" (days)*	132	212	37.8	<0.1
Patients dragged from previous months	36	37	2.7	ns
Deaths (%)	11.1	10	-1.1	ns

*Day without antibiotic therapy; data includes January 2004.
** Mann-Whitney analysis

RESULTS

A total of 180 patients and 107 patients were included in the 2002 and 2003 surveys, respectively. The demographic data of all the participants are shown in Table 1. No statistical differences were observed in the two periods related to percentage of patient death and patients dragged from the previous month. More subjects (40.6%) were surveyed in 2002, while 37.8% more antibiotic-free days (therapeutic window) were registered in 2003. One-hundred thirty-three and 38 subjects ($p<0.01$) received less that one antibiotic course during their admission in the Intensive Care Unit. Table 2 shows the admission diagnosis and the total number of antibiotic exposures/diagnosis.

Table 2. Admission diagnosis and total antibiotic exposures/diagnosis

DIAGNOSIS	2002	2003	Δ%
Pneumonia	115	92	-20
Pancreatitis	12	32	62.5
Trauma	99	146	32.2
Sepsis	39	82	52.4
Abdominal infections	19	5	-73.7
Intestinal vascular diseases	7	12	41.7
Respiratory failure	20	19	-5
CNS injuries	13	12	-7.7
Burn grade III	21	15	-28.6
Others	21	38	44.7

There was no difference between the study periods; data includes January 2004 (p=0.06; Mann-Whitney).

In 2002, the 180 patients had 375 antibiotic exposures: piperacillin-tazobactam; imipenem; vancomycin; ceftriazone (13.8%; 11.2%; 10.1%; 9%) were the four most prescribed medications. In 2003, the 107 subjects had 453 antibiotic exposures. The same medications were placed at the top of the list but in a different proportion: piperacillin-tazobactam - 9.2%; imipenem - 11.3%; vancomycin - 12.6%; ceftriaxone - 9%. Ninety-six percent and 94% of the treated subjects in the 2003 and 2002 periods received their antibiotics intravenously.

A net increment in total antibiotic cost was observed during the 2003 Infectious Disease Specialist intervention period ($p>0.1$) compared to the 2002 period (Tables 3). The differences between DDD and cost in both periods were not statistically significant, while the mean Drug Utilization 90% Index (DU90% Index) was significantly different between the two periods ($p=0.02$)

The individual antibiotics DU90% index including costs prescribed in this survey during 2002 and 2003 are shown in Tables 4 and 5. During the 2003 intervention period, there was an increment of 28.4% in the individual expenses of imipenem/cilastin, piperacillin-tazobactam and ampicillin-sulbactam, while ciprofloxacin and ceftazidime decreased by 14.2% in comparison to the 2002 period.

Table 3. Define daily dose (DDD), Drug utilization index 90% (DU 90%) and total cost analysis (Pareto Analysis)

Month	DDD-2002	DDD-2003	Cost-2002*	Cost-2003*
August	54.88	51.76	6029	1694
September	336.68	419.08	44,196	46,763
October	396.79	504.6	46,791	53,805
November	666.91	750.6	62,118	63,267
December	575.89	599.85	47,975	58,952
January 2004		384.39		34,700
Total	2031.15	2710,28	207,109	259,181
Average	406.23	451.71	41,422	46,196.83
SD	235.23	236.48	20,978	22,676
	DU90%-2002	DU90%-2003	Cost-2002*	Cost-2003*
August	48.97	45.8	5984	1055
September	297.73	373.76	39,730	39,223
October	359.97	439.97	44,238	49,022
November	536.62	682.18	54,467	58,362
December	534.28	537.9	45,690	53,462
January 2004		372.74		31,222
Total	1777.57	2452.35	190,109	232,346
Average	355.51	408.72	38,021.97	38,724.33
SD	201.3	212.91	18,689	20,901.63

1. Cost and DU 90% data is presented including January 2004

* Cost is in NIS (New Israel Shekel)

SD= Standard deviation

Table 4. Individual antibiotic drug utilization index (DU 90%) – 2002

Antibiotic Name	DU90%	grs	Cost NIS[2]
Ampicillin-Sulbactam	**218.7**	**874.5**	**31,191.00**
Ciprofloxacin	**194.22**	**90.8**	**18,956.00**
Imipenem/Cilastin	**183.67**	**332**	**49,636.50**
Vancomycin	**169.65**	**335**	**10,720.00**
Piperacillin-Tazobactam	**151.22**	**1853.5**	**33,845.50**
Ceftriaxone	**148**	**356**	**1,444.00**
Metronidazole	**114.98**	**159.67**	**1,044.00**
Erythromycin (IV)	**114**	**114**	**7,638.00**
Cefipime	**69**	**144**	**8,579.00**
Amoxicillin-Clavulanic Acid	**67.59**	**185**	**5,157.00**
Colestin	**67**	**201MU[3]**	**1,776.50**
Amhotericin B	**57.86**	**2.025**	**2,891.00**
Fluconazole	**54**	**8.2**	**4,551.00**
Penicillin	**53.94**	**190 MU[3]**	**1,691.00**
Ceftazidime	**47.44**	**178.25**	**11,275.00**
Ampicilin	**46**	**92**	**1,012.00**
Cefazoline	**41.17**	**121**	**447**
Acyclovir	1.65	5.85	445
Amikacin	27.75	86.25	1,467.50
Cefuroxime	2.75	8250	83
Clindamycin	10.01	18	780
Cloxacilin	27.5	55	3,163.00
Erythromycin (PO)	27.55	24.65	27.64
Gancyclovir	2	1250	515
Gentamycin	28.5	6.56	117
Levofloxacin	38	9.5	3,743.00
Neomycin	8	8	100
Nistatin Oral	0	0	0
Ofloxacin	2.5	1.2	435
Nistatin Oral	0	0	0
Resprim (IV)	20	40	1,180.00
Rifampicin	9	5.4	36

1. Bold letters indicate 90% of all the prescribed antibiotics
2. NIS = New Israel Shekel
3. MU = Mega Units

Table 5. Individual antibiotic drug utilization index (DU 90%) – 2003

Antibiotic name	DU90%	grs	Cost NIS[2]
Ampicillin-Sulbactam	**616.88**	**1264**	**45,083.00**
Vancomycin	**354.87**	**667**	**21,344.00**
Imipenem/Cilastin	**266.79**	**476.85**	**71,290.00**
Ceftriaxone	**201.26**	**366.5**	**2,913.60**
Ciprofloxacin	**192.49**	**78.2**	**16,324.50**
Piperacillin-Tazobactam	**178.75**	**2281.5**	**47,658.65**
Metronidazole	**108.97**	**171.25**	**1,082.08**
Colestin	**88**	**266MU[3]**	**2,439.20**
Ceftazidime	**74.5**	**228**	**9,614.02**
Amoxicillin-Clavulanic Acid	**69.32**	**216**	**5,904.02**
Fluconazole	**59**	**11.4**	**6,327.00**
Cefuroxime	**55.5**	**27.75**	**185**
Penicillin	**50.5**	**209MU[3]**	**537**
Cefazoline	**44.98**	**132**	**484.69**
Acyclovir	4.07	8.25	527.25
Amikacin	37.5	35.5	603.55
Ampicilin	4.75	9.5	99
Aztronam	8	32	1,178.67
Azithromycin	29.66	8	1,472.00
Cefadroxil	4	8	0
Cefipime	32.5	65	8,372.00
Cloxacilin	23	46	661.25
Ertapenem	39.25	48.25	11,773.00
Gentamycin	13.68	3.04	54.83
Levofloxacin	10	5	1,970.00
Meropenem	17.25	34.5	5,175.00
Nistatin Oral	2	3MU[3]	20
Resprim	9.8	3.92	236
Roxithromycin	12.5	3.75	29.25

1. Bold letters indicate 90% of all the prescribed antibiotics
2. NIS = New Israel Shekel
3. MU = Mega Units

The over-all bacteriology analysis is depicted Table 6. The Infectious Diseases Specialist intervention brought an increment in the number of blood cultures (increased by 36%) sent to the laboratory. Five percent and 15.6% of the blood cultures in 2002 and 2003 were positive for Acinetobacter spp; positive blood cultures for Serratia spp were in 2.4% and 9.1% for 2002 and 2003, respectively. Pseudomonas Aeroginosa in blood cultures increased by 5.4% when comparing 2002 to 2003 (29.6% vs 31.2%).

Table 6. Bacteriology summary

Bacteriology	2002	2003	pvalue
Blood cultures	706	1109	
a. Positive	83	109	
b. Contaminated	24	79	
c. Negative	599	921	
d. Appropriateness	89%	87%	p>0.1
Other cultures	441	345	
a. Positive	232	165	
b. Contaminated	1	8	
c. Negative	208	172	
d. Appropriateness	80%	88%	p>0.1
Integrated Appropriateness	83.3%	87.2%	p>0.1

(*) Data includes January 2004.

The integrated appropriateness for total positive cultures for the non-intervention 2002 period was 83.3%, and 87.2% for the intervention 2003 period, respectively (p>0.1).

When cost analysis was performed in relation to 100 admission days (Table 7), it was established that the Infectious Diseases Specialist intervention result is an increment in 550 NIS(median) /100 admission days cost.

Table 7. Total and Median Antibiotic Cost / 100 admission days during both study periods

	2002	2003	p[#]
Total number of admission days	1381	1863	0.12
Total cost (NIS*)	207,109.5	259,181	0.93
Median Total Cost/100 admission days (CI95%)	13,310 (11,110;18,420)	13,860 (6,710;18,020)	0.66

(*) Costs are in NIS (New Israel Shekel)
(**) Data includes January 2004.
(#) Mann-Whitney Analysis

DISCUSSION

In this descriptive prospective and retrospective longitudinal rather than point prevalence survey on antibiotic prescription pattern in a general intensive care unit located in a university medical center, was demonstrated that 95% and 82.5% of surveyed individuals had at least one antibiotic exposure in the prospective and retrospective periods. The interventional policy brought an increment of 36% in blood cultures sent to the laboratory. It is known that the more blood cultures sent to the laboratory, the better are the conditions for identifying microbial pathogens with a subsequent later decrease in antibiotic cost.[17] A 20% net increment in total antibiotic cost was observed during the Infectious

Disease Specialist intervention period in comparison to the non-interventional periods. However, when cost analysis was performed considering the admission/days (total cost /100 admission days), the Infectious Disease Specialist intervention increased the median cost by 550 NIS / 1000 admission days in this General Intensive Care Unit.

The non-significant integrated appropriateness difference of 4% between both periods for all positive bacterial cultures stressed the positive contribution of an Infectious Disease Specialist intervention, as the 'watch-dog' of existing protocols for antibiotic therapy.

Hanssens et al[18] reported that 74% of patients admitted to a medical intensive care unit were treated with antimicrobial medications. A prospective antibiotic utilization survey performed in two different medical departments showed that 35.3% and 39% of the acute admitted patients had at least one antimicrobial exposure.[19]

Ninety-six percent and 94% of the treated subjects in the 2003 and 2002 periods received their antibiotics intravenously; in the remaining patients the enteral route (nasogastric tube) was indicated, especially when metronidazole or quinolones were prescribed. It can be sustained that both study periods were similar because of a failure to demonstrate some differences between the groups in respect to patient death, admission diagnosis case mixing and total admission days included in this survey.

The existing link between the over- or improper use of antibiotics in different admission set-ups and the development of antibiotic resistance is well known.[20-22] Some 30-50% of patients received antibiotic therapy without any clinical indications. In some countries, antibiotics can be obtained as OTC medications.[23]

The concept of antibiotic class cycling has been advocated as a potential strategy for reducing the emergence of antimicrobial resistance.[6,7] During the 2002 and 2003 periods, 74% and 35% of the treated subjects did not complete one antibiotic course, these results do not indicate a rotating/cycling intervention, although it is possible to assume that the active intervention of the specialist stopped the unnecessary use of antibiotics.

The present results were not expected to be in accordance with other publications[24,25] considering the principle of geographic-specific antimicrobial therapy[7], except for the utilization of ceftriaxone in both periods, similar to data published by others.[24,26]

In a neurological intensive care unit, it was demonstrated that a reduction of 44% in antibiotic expense can be reached without jeopardizing patient wellbeing or increasing morbidity and/or mortality.[27]

The appropriateness found for positive blood cultures established in both periods of this study is in accordance with Erbay et al[24] who found 85% appropriateness with the intervention of the Infectious Disease Specialist in comparison to 25% appropriateness when other physicians prescribed antibiotics for patients admitted to one intensive care unit. These authors did not include short admissions (less/up to 24 hours). Non-appropriate antibiotic prescription was established at 18% up to 65%.[27,28]

Using a different set-up, it has been demonstrated that the intervention of a physician specialist in Clinical Pharmacology was effective in reducing antibiotic costs by 51% when a prescription-point prevalence analysis was performed for comparison between two internal medical departments.[19]

The limitations of this study were: 1) patient outcomes were not recorded in the prospective part of the survey; 2) the use of prophylactic antibiotic therapy in both periods was not registered; 3) emergence of bacterial resistance was not investigated and 4) the modified Kunin criteria for appropriateness were not taken into consideration.[29]

In institutions fortunate enough to have the services of an Infectious Diseases Specialist, it has been established that cooperative efforts among the medical and administrative staffs should lead to early and, preferably, mandatory consultations for patients with bacteremia.[30,31] Recently, Biswal et al[32] concluded that there is a tremendous impact of antibiotic use on the cost of therapy in the intensive care unit.

The medical team is the determinant factor for Infectious Disease Specialist advice[8] or strategies[6,7] established to control excessive antibiotic use and the development of antibiotic resistance. The most indicated strategy would be a multidisciplinary approach involving cooperation between infection control, nursing, pharmacy and medical staffs. These programs should focus on promoting expenses and infectious control, with rational antibiotic prescription and utilization aimed at minimizing the future emergence of bacterial resistance.

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