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Utilization Pattern of Antibiotics in Different Wards of Specialized Sari Emam University Hospital in Iran

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Abstract: The main goal of this study was to compare the utilization of antibiotics in different wards of a university hospital. Consumption of antibacterial drugs rose dramatically during years 2000-2005 in Iran. Data collected during first half of year 2000 and 2005 in Emam University Hospital in city of Sari in Iran, showed use of antibiotics jumped from 95.4 DBDs (Defined Daily Doses per patient's bed-days) to 124 DBDs. Distribution of different class of anti-microbial showed highest increase in use of vancomycin with 28.4 folds and clindamycin with 4.8 fold. Use of cotrimoxazole, aminoglycosides and tetracyclines remained fairly unchanged during this period. However, during the same period, consumption of penicillin G, aminopenicillins and cloxacillin dropped 10.3, 3.8 and 3 fold, respectively. Among university hospital departments, oncology ward followed by ICU and general surgery consumed the most antibacterial agents in year 2000. In year 2005, ICU ward followed by gynecology, oncology and orthopedic were among the University Hospital Departments with highest consumption of antibiotics. The most highly used antibiotics in year 2000 were cefazolin followed by ampicillin, ceftizoxime and gentamicin. In year 2005, cefazolin, ceftriaoxone, gentamicin and ciprofloxacin were the most prescribed antibiotics. Injectable antibiotics accounted for 51.8 and 79.4% of total DBDs in first half of years 2000 and 2005, respectively. The bulk of prescription (90% of total DBDs) was made up of 13 out of 32 total antibiotic types in 2000 and 11 out of 29 total antibiotics types in 2005. Comparing with similar hospitals in other countries, data presented show a dramatic increase in antibiotics prescribed by physician in Emam University Hospital.

Key words: Antibiotic, training hospital, DDD, defined daily dose, utilization pattern

INTRODUCTION

Pharmacy used to be limited to formulation of drugs. However, due to irrational drug prescription and its health and economic consequences, evaluation of rational use of drug seemed to be necessary. Antibiotics are among the most common drugs prescribed in hospitals today. As consumption of antibiotics rises, resistance to antibiotics became a major threat to public health. Existing evidence suggest that there is a causal association between anti-microbial usage in hospitals and anti-microbial resistance (Rogues *et al*., 2004; De With *et al*., 2006; Dancer *et al*., 2006). Some papers recommend that hospitals should monitor both anti-microbial use and susceptibility trends in an attempt to reduce emergence and spread of anti microbial-resistant pathogens (Rogues *et al*., 2004). International efforts are needed to counteract the growing problem of anti-microbial resistance (Wise *et al*., 1998; Cars *et al*., 2001). Today, the biggest risk factor for antibiotic resistance is irrational use of this drug among ordinary people (Melander *et al*., 2000). No public data is available on sale of antibiotics around the world. As a result it would not be possible to make any comparison on production, distribution, sale and usage of antibiotic internationally. Drug utilization research can provide useful information to health care providers and policy makers. It offers the prospect of improving the quality of pharmacotherapy, gaining insight in volume and cost development of drug use and estimating prevalence and incidence of disease rather than drug use (Mantel-Teeuwisse *et al*., 2001).

Due to antibiotic's large share in drug expenditures and special adverse effects such as microbial resistance, excess use of antibiotics became an issue of particular concern in Iran. This study evaluates the use of antibiotics in Sari Emam university hospital in north of Iran. Data collected based on Defined Daily Dose (DDD) methodology are standardized and allow best comparisons for antibiotics use between various hospitals and among different wards (Natsch *et al*., 1998).

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MATERIALS AND METHODS

Goals of this study were to compare the utilization of antibiotics in different wards of a university hospital and to report the correlation between antibiotic consumption and resistance patterns based on our previously published papers (Mahdavi *et al*., 2006; Ebrahimzadeh *et al*., 2005a, b, 2006).

Utilization pattern of antibiotics in different wards of Emam university hospital were reviewed for over two periods, first half of years 2000 and 2005. With the difference that in 2005, heart and CCU wards were replaced by orthopedic. In order to do a standard repeatable DUR (Drug Utilization Review), data were collected as Defined Daily Dose (DDD), according to Anatomic Therapeutic Chemical classification system (ATC/DDD). This system is described by WHO in collaboration with center for drug statistics methodology (WHO, 2000). Defined daily dose is a unit based on the average daily dose used for main indication for consumption of certain medication. Only antibiotics for systemic use (Anatomic Therapeutic Chemical J01) were included in the subsequent analysis. Other anti-infectious pharmaceuticals such as topical dermatological, ophthalmological or otolaryngological were not included in this study. For easier comparison, amount of antibiotic (in gram) was converted to unit of Defined Daily Dose (DDD). Antibiotics marketed both alone and in form of combinations (e.g., trimethoprim and sulphonamides), amounts of individual compounds were accounted for separately. For antibiotics combined with a β-lactamase inhibitor, only amount of antibiotic was included. In addition to the total usage in DDD, a relative parameter, DBDs was also used. DBD is the number of defined daily doses per patient's bed-days during the observation period. It is computed using the following formula (Kolar *et al*., 2001):

$$\text{DBDs} = \frac{\text{DDD}}{\text{No. of bed-days}} \times 100$$

Three hundred and twenty four hospital beds were assigned to this study. During the study period, level of hospital hygiene and measures for infection control remained unchanged.

RESULTS

Numbers of patient's bed-days in Sari Emam university hospital during this study were 27661 in first half of 2000 and 32295 in first half of 2005 (Table 1, 2). Consumption of antibiotics in the university hospital increased from 95.4 in 2000 to 124 DBDs in 2005. Highest increase was found in Vancomycin with 28.4 fold (0.12 DBDs for first half of 2000 vs. 3.41 DBDs for first half of 2005) and clindamycin with 4.8 fold increase (1.08 vs. 5.17 DBDs). Cefazolin was the most consumed antibiotics in first half of year 2000 and 2005 with 20.5 vs. 40.00 DBDs, respectively (2 fold increases). Use of third generation cephalosporines increased 1.9 fold (12.12 vs. 23.18), ciprofloxacin showed 3-fold increase (2.95 vs. 8.83 DBDs) and Erythromycin showed 3.3-fold increase (1.75 vs. 5.79 DBDs). Use of cotrimoxazole, aminoglycosides and tetracyclines remained fairly unchanged. On the other hand, 10.3-fold reduction was observed in Penicillin G consumption (3.18 vs. 0.31 DBDs), 3.8-fold reduction in aminopenicillins (21.44 for vs. 5.26 DBDs) and 3-fold reduction in cloxacillin use (3.18 vs. 1.03 DBDs).

Table 1: Use of antibiotics based on DBDs in first half of 2000

Antibiotics	Emerg.	Oncolo.	Intern.	Urolo.	Heart	CCU	ICU	B. surg.	Gen. surg.	Gynec.	Newborns	Sum
Aminoglycosids	14.17	35.92	8.78	20.18	1.32	2.76	28.02	6.66	20.74	8.24	6.30	13.10
Aminopenicillins	6.93	4.21	18.43	13.70	19.14	13.14	11.67	3.62	29.64	55.81	5.76	21.44
1st gen. Cepha	21.46	8.26	10.75	62.48	5.33	8.77	45.20	26.43	36.23	46.26	0.40	25.75
3rd gen. Cepha	10.99	46.77	26.72	5.73	4.77	5.93	39.37	4.92	5.27	0.35	0.09	12.12
Chloramphenicol	5.37	0.08	0.03	1.67	0.00	1.41	3.31	2.30	16.47	0.46	0.00	3.50
Ciprofloxacin	0.16	27.32	2.05	2.14	0.41	0.23	6.50	1.13	0.07	0.00	0.00	2.95
Clindamycin	0.34	3.56	3.59	0.00	0.00	0.56	4.60	0.09	0.25	0.03	0.00	1.08
Cloxacillin	0.42	27.22	2.46	0.00	0.00	0.23	14.10	0.04	0.95	0.14	0.84	3.18
Cotrimoxazole	0.25	5.04	3.30	5.22	2.36	0.72	0.00	0.75	0.37	0.23	0.00	1.76
Tetracyclines	0.00	0.28	0.75	2.24	0.00	0.00	0.00	1.23	0.27	0.05	0.00	0.48
Erythromycin	0.29	7.07	3.51	0.40	1.02	0.46	0.00	0.00	2.44	0.61	0.00	1.75
Metronidazole	1.90	12.88	6.94	0.90	0.27	2.04	9.87	1.21	6.54	1.06	0.04	4.01
Penicillin G	3.10	2.96	5.10	1.50	4.64	1.06	14.56	4.61	2.07	4.10	0.00	3.18
Penicillin V	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.11	0.00	0.04
Piperacillin	0.00	6.49	0.21	0.00	0.00	0.13	0.00	0.00	0.23	0.00	0.00	0.58
Rifampin	0.11	1.36	0.60	0.50	0.00	0.00	0.60	0.74	0.05	0.00	0.00	0.33
Vancomycin	0.00	0.59	0.16	0.00	0.00	0.00	0.30	0.22	0.10	0.00	0.02	0.12
Sum	65.49	190.01	93.38	116.67	39.26	37.44	178.10	53.89	121.67	117.45	13.45	95.37

Table 2: Use of antibiotics based on DBDs in first half of 2005

Antibiotics	Emerg.	Oncolo.	Intern.	Urolo.	Orthop.	ICU	B. Surg.	Gen. Surg.	Gynec.	Newboms	Sum
Aminoglycosids	9.83	26.49	6.68	24.18	23.68	30.09	9.50	21.26	9.04	5.11	15.83
Aminopenicillins	0.70	3.71	5.21	1.15	0.98	6.09	1.62	1.85	16.59	15.00	5.26
1st gen. Cepha.	30.90	2.65	2.04	35.83	72.05	46.03	44.11	39.35	108.34	0.00	43.80
3rd gen. Cepha.	25.87	50.19	48.58	13.87	6.12	83.01	20.31	12.42	2.66	0.34	23.18
Ciprofloxacin	2.11	9.75	15.36	3.69	13.18	27.70	5.98	4.96	0.51	0.00	8.83
Clindamycin	2.36	8.36	6.95	1.44	4.78	20.27	2.45	5.44	1.31	0.00	5.17
Cloxacillin	0.36	1.10	3.23	0.11	0.95	1.17	0.16	0.21	0.05	0.12	1.03
Cotrimoxazole	0.00	27.70	16.00	6.80	0.00	0.80	0.80	1.40	0.80	0.00	1.69
Tetracyclines	0.00	0.90	0.42	0.70	0.09	0.56	0.43	1.10	3.32	0.00	0.73
Erythromycin	3.38	9.75	17.78	1.82	0.95	9.82	0.77	1.73	1.43	0.00	5.79
Metronidazole	7.66	4.13	6.87	1.11	3.47	36.06	3.30	19.47	3.82	0.05	8.96
Penicillin G	0.19	0.02	0.31	0.00	1.41	0.00	0.40	0.00	0.13	0.00	0.31
Vancomycin	0.79	17.56	2.75	0.20	3.63	18.19	7.03	1.04	0.03	0.66	3.41
Sum	84.15	135.15	116.20	84.10	131.30	278.99	96.11	107.83	147.26	21.28	124.00

Among university hospital departments, oncology ward followed by ICU, general surgery, urology were the most antibacterial consumer in first half of the year 2000. In first half of the year 2005, ICU ward followed by gynecology, oncology and orthopedic were among the highest consumers of antibiotics. The rate of use of antibiotics among hospital departments varied from 21.3 DBDs for newborns to more than 278 DBDs for ICU in first half of 2005. Table 1 and 2 show DU (Drug Utilization) 90% approach in our hospital. The bulk of prescriptions (90% of total DBDs) were made up of 13 out of 32 possible antibiotics types available in 2000 and 11 out of 29 possible antibiotics types available in 2005. From the list of antibacterial agents prescribed during first half of the year 2000, cefazolin was the most highly used, followed by ampicillin, ceftizoxime and gentamicin. For the same period of year 2005, cefazolin, ceftriaoxone, gentamicin and ciprofloxacin were the most highly used antibiotics. From total of 32 types of antibacterial agents used during first half of the year 2000, Penicillin V was the least anti microbial used with 0.04 DBDs. In the list of 29 different types of anti microbial agents prescribed during the same period of year 2005, Penicillin V was the least prescribed, with 0.01 DBDs. Injection were the popular method to administer the antibiotics in Emam university hospital both in terms of DDD consumption and prevalence of use. Injectable antibiotics accounted for 51.8 and 79.4% of total DBDs in first half of the years 2000 and 2005, respectively.

DISCUSSION

The relationship between consumption of antimicrobial agents in humans and the emergence of resistance in bacteria is complex and finding an association between them has proved difficult to establish. Other contributing factors include cross-transmission, inter-hospital transfer of resistance, a community contribution to resistance, or a complex relationship between resistance and the use of a variety of antibiotics (Melo Cristinio, 1999).

Until today no data were available on consumption of antibiotics in Iranian hospitals. Data collected for this research on use of antibiotics shows that consumption of Benzyl and Phenoxymethylpenicillin were very low. These drugs were used despite some opposition, for initial treatment of pneumonia, due to remaining favorable susceptibility. In early 2000 increase in Penicillin resistance among *Staphylococcus* sp. (*Aureus* and *Coagulase negative*) and *Streptococcus* sp. were reported in Sari. In response, policies regarding inpatient antibiotic therapy were changed and nationwide alert issued calling to reduce use of Penicillin G. Consumption of Penicillin G decreased from 3.18 DBDs in year 2000 to 0.31 DBDs in year 2005 (about 10.3 fold decrease). Change in consumption was followed by decrease in Penicillin resistance cases among *Staphylococcus* sp. (*Aureus* and *Coagulase negative*) from one fourth of isolated cases in 2000 to one fifth of isolated cases in 2005. Similar results observed among *Streptococcus* sp. from 41.7% reduction of antibiotic resistance in 2000 to 35.7% of antibiotic resistance in 2005 (Mahdavi *et al*., 2006; Ebrahimzadeh *et al*., 2005a). Penicillin V was the least prescribed anti microbial during this study periods. In Denmark, penicillin V was the most used antibiotic, representing almost half of the prescriptions, followed by amoxicillin. In Italy, prescription was split among a greater number of compounds, with amoxicillin and the combination of amoxicillin plus enzyme inhibitors in the first two places (Vaccheri *et al*., 2002). In 49 French hospitals, Penicillin's were the most frequently prescribed antibiotics (Rogues *et al*., 2004). Germany shows the same results (De With *et al*., 2006; With *et al*., 2004). Taiwan reported an 8.8 fold increase in usage of β-lactam and β-lactamase inhibitor combinations in 2003 (19.55 DDD per 1000 patient-days) compared with (2.22 DDD) in 1994 (Hsueh *et al*., 2005). ICU ward of a university hospital in Scotland reported high usage of β-lactam (110.59 DBDs) (Dancer *et al*., 2006).

In Sari Emam University hospital consumption of cephalosporins was 67 DBDs in 2005. This rate of usage for cephalosporins is relatively high. Consumption of this

agent was only 0.3 DBDs in Finland, less than 0.1 DBDs in Norway and close to zero in Denmark (Bergan, 2001). The rate of resistances to eight most frequently isolated bacterial pathogens (including *E. coli*, *Klebsiella*, *Proteus* and *P. aeruginosa*) to Cephalosporins in Sari was low (Mahdavi *et al*., 2006; Ebrahimzadeh *et al*., 2006). There were no uses of new macrolides (azithromycin, roxithromycin and clarithromycin) but consumption of Erythromycin increased from 2000 to 2005. ICU ward of a university hospital in Scotland reported 34.02 DBDs (Dancer *et al*., 2006).

So far, in Iran, vancomycin is the only antibiotic which human pathogen did not develop resistance to. Use of vancomycin should be restricted carefully to ensure, the usually susceptible Gram-positive organisms remain susceptible. In 2005, vancomycin resistance was detected in 1.3% of the *Staphylococcus* sp. (*Aureus* and *Coagulase negative*) and 1.1% of *Streptococcus* sp. isolates in sari (Mahdavi *et al*., 2006).

High usage of Trimethoprim/Sulphamethoxazole in 2000 could explain the high prevalence of *E. coli* resistance to it [48.1% (Ebrahimzadeh *et al*., 2005b)]. In 2005 level of resistance to Trimethoprim/ Sulphamethoxazole reduced by 10% even though usage of this antibiotic remains unchanged (Mahdavi *et al*., 2006). Because of differences in local resistance patterns and modes of antibiotic usage, local and hospital surveillance programmes are needed for elaboration of local directives for rational antibiotic use and hospital infection control. The spectrum of antibiotics use changed dramatically. There was a trend to replace narrow spectrum antibiotics with broader spectrum ones. Especially increased was the consumption of cephalosporins and fluoroquinolones. Thus the pressure increased on both Gram-positive as well as Gram-negative micro-organisms. Until recently there were no official restrictions or guidelines for antibacterial prophylaxis and therapy in our hospital. This situation gave us an opportunity to analyze the changes in resistance patterns together with changes in antibiotic use.

ICU is one of the university hospital wards with high level of antibiotic resistance. Uses of antibiotics in ICU were reported by Malacarne *et al*. (2004), Walther *et al*. (2002), Sintchenko *et al*. (2005) and Petersen *et al*. (1999). Data collected during first half of year 2005 in Emam university hospital shows antibiotic consumption of 279 DBDs. The other two wards in Emam University Hospital with high consumption of antibiotics were Gynecology with 147.2 and Oncology with 135.2 DBDs. Data presented proves that consumption of antibiotics in ICU ward were twice the other two wards for the same period. ICU wards of all university hospitals in Germany reported antibiotic use of 140 DDD/100 patients-days (De With *et al*., 2006). A separate study reported an average antibiotic use of 146 DDD/100 in Intensive Care Units (ICUs) surgery and 187 DDD/100 in department of medicine of eight university hospital in Germany (With *et al*., 2004).

DBDs do not give precise details of the practice of antibiotic administration in local institutions that might have significant influence on the emergence of resistance. The use of sub-optimal doses, unreasonable duration of prophylaxis and the effect of drug combinations are some examples of such practices on which we have no information about it. Evaluation of these factors in some departments such as ICUs where patients simultaneously receive several different antibiotics is even more difficult. In Emam university hospital, injection was the most frequently used method to administer the antibiotic. Inject able antibiotics accounted for 51.8 and 79.4% of total DBDs in first half of 2000 and 2005, respectively. However, in Italy and Denmark, antibiotics were mostly administered orally both in terms of DDD consumption and prevalence of use. In Italy, inject able antibiotics accounted for only 4% of total DDDs. Data showed in Denmark, use of inject able antibiotics was negligible (Vaccheri *et al*., 2002).

In conclusion, these findings have implications for local antibiotic policies, infection control and cleaning schedules and could provide impetus to generate better policies for use of antibiotic in health care system. Clinicians should consider the consequences of prescribing anti microbial as part of an overall commitment towards basic hygiene and infection control in their wards. Comparison of data collected from Emam university hospital with similar hospitals in other countries showed consumption of antibiotic in Sari Emam university hospital was higher. Limited variety of antibiotics was available in Emam university hospital during the research periods. This study proved that there is an urgent need for national drug policies and drug education program for health care professionals. Further comparative studies are also needed in order to obtain a map of the use of antibiotics in human medicine in relation to the resistance pattern. As highlighted in the beginning, an association between changes in the prevalence of resistant microorganisms with the use of antimicrobials is difficult to establish. However, despite the multifactorial nature of antibiotic resistance the central issue remains quite simple: the more you use it, the faster you lose it.

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