Assessment of antibiotics use after introducing a hospital formulary by ATC/DDD methodology

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Abstrak

Tujuan penelitian ini ialah untuk membandingkan penggunaan antibiotik sebelum dan sesudah penerapan Formularium Rumah sakit (FRS) di Rumah Sakit MMC (RS MMC). Seluruh penggunaan antibiotik yang termasuk dalam klasifikasi J01 Anatomical Therapeutic Chemical (ATC) dicatat dari data pelayanan farmasi rawat-inap dan rawat-jalan. Paramater kuantitatif penggunaan antibiotik pasien rawat inap adalah Defined Daily Doses/100 hari rawat (DDDs/shr) dan DDDs/1000 pasien/hari (DDDs/rph) untuk pasien rawat-jalan. Parameter kualitas penggunaan obat adalah jumlah nama obat yg berdasarkan urutan DDDs membentuk segmen 90% dari total penggunaan obat (DU90%) dan kepatuhan peresepan antibiotik terhadap formularium dalam segmen DU90% berdasarkan nama dagang dan nama generik. Kuantitas dan kualitas penggunaan antibiotik dibandingkan sebelum dan sesudah penerapan FRS (tahun 2000 terhadap tahun 1999). Analisa perbandingan kuantitas penggunaan antibiotik dilakukan dengan. uji peringkat tanda Wilcoxon. Penggunaan antibiotik untuk pasien rawat-inap menurun nyata sebesar 23,1%, dari 124,96 DDDs/shr di tahun 1999 menjadi 96,13 DDDs/shr (p= 0,03). Penurunan penggunaan antibiotik di rawat-jalan 4,9%, dari 3,49 DDDs/rph di tahun 1999 menjadi 3,32 DDDs/rph di tahun 2000 (p=0,58). Siprofloksasin adalah antibiotik yang terbanyak diresepkan di rawat-inap pada tahun 1999 dan 2000, sedangkan di rawat-jalan amoksisilin pada tahun 1999 dan siprofloksasin pada tahun 2000. Kepatuhan peresepan antibiotik terhadap FRS untuk pasien rawat-inap dan rawat-jalan berturut-turut berdasarkan nama generik 100% dan 100%, berdasarkan nama dagang 90,5% dan 94,3%. Profil penggunaan antibiotik dalam segmen DU90% untuk pasien rawat-inap dan rawat-jalan dapat dikatakan tidak menunjukkan perbaikan baik berdasarkan nama dagang maupun nama generik. Sebagai kesimpulan ialah bahwa penerapan FRS di RS MMC hanya menunjukkan penurunan bermakna pada penggunaan antibiotik untuk pasien rawat-inap. ***(Med J Indones 2004; 13: 173-9)***

Abstract

The objective of this study is to compare the use of antibiotics at the Metropolitan Medical Center Hospital in Jakarta, Indonesia (MMCH), before and after the implementation of a hospital formulary. All antibiotic data under J01 Anatomical Therapeutic Chemical (ATC) classification were collected from pharmacy inpatient and outpatient records. Quantitative antibiotic use was expressed in Defined Daily Doses/100 bed-days (DDDs/hbd) for inpatients and DDDs/1000 patients/day (DDDs/tpd) for outpatients. The general quality of drug use was assessed in number of drugs that account for 90% of the use (DU90%) and the adherence to hospital formulary by substance and brand name within the DU90% segment. Quantitative and qualitative antibiotic use were compared before and after implementation of the formulary (1999 to 2000). The Wilcoxon rank sign test was used to compare overall antibiotic use. Inpatient antibiotic usage decreased significantly by 23.1%, 124.96 DDDs/hbd in 1999 to 96.13 DDDs/hbd during 2000 (p= 0.03) and outpatient antibiotic usage decreased insignificantly by 4.9%, 3.49 DDDs/tpd during 1999 to 3.32 DDDs/tpd during 2000 (p=0.58).The most commonly antibiotic use was ciprofloxacin in inpatient setting during the study and in out-patient setting was amoxicillin in 1999 and ciprofloxacin in 2000. The adherence to the formulary by substance and by brand name in inpatient department was 100% and 90.5% and in outpatient department was 100% and 94.3% during the study. DU 90% by substance name and by brand name was considerably not improved in both settings. The conclusion is that the effectiveness of one year formulary implementation at MMCH was only revealed in inpatient setting. ***(Med J Indones 2004; 13: 173-9)***

Keywords: antibiotic use, hospital formulary

Antimicrobial use is the key driver of resistance, which comes from a combination of overuse, misuse and under use.[1,2] Increased antibiotic use in the hospital is often associated with increased frequency of resistance.[3-5] The antibiotic usage patterns exert a significant influence over the rates of resistance

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observed in multidrug-resistant nosocomial pathogens.[3,6] The increased resistance has increased the morbidity and mortality in many patients and it has also increased the cost of treatment.[1,4,5] Moreover, the proportion of inappropriate antimicrobial use in the hospital was more than 30%.[2,7]

The contribution of developing countries to world consumption, and consequently to the problem of resistance is not negligible: 35% of the total health budget is spent on antimicrobials. Factual data of antimicrobial use in developing areas are scanty. Control of antimicrobial use in hospital and clinic of many developing countries is lacking or poor.[4]

Formulary control was one of the considered successful strategies to improve antimicrobial use.[1,7,8] Strict adherence to well-accepted infection control guidelines, along with caution in use of broad-spectrum antimicrobial agents, represents the best strategy for preventing the emergence and spread of nosocomial multidrug resistance.[6]

Although rational drug use has been promoted in Indonesia for a long time[9] but still more than 40% of patients receive antibiotics in primary health care, perhaps twice than what is clinically needed.[2] The public hospital had to issue a formulary as a prescribing guideline.[9] However, only the public hospitals and not the private hospitals, have strictly applied the policy. In 1999, with the hospital accreditation system, all hospitals were encouraged to develop policies and procedures that promote rational drug use by publishing clinical practice guidelines (CPGs) and a hospital formulary and by the formation of a nosocomial surveillance committee.[10] Nevertheless, drug utilization research is generally scarce in Indonesia, and little is known about the use of antibiotics related to the Anatomical Therapeutic Chemical / Defined Daily Dose (ATC/DDD) methodology.

Based on these considerations we compared the use of antibiotics at the Metropolitan Medical Center Hospital (MMCH), a private hospital in Jakarta, Indonesia, before and after the implementation of a hospital formulary. In order to perform a standardized and international comparison the ATC/DDD methodology was used. The quantity indicator that was used are DDDs/100 bed-days for inpatients and DDDs/1000 patients /day for outpatients.[11] Drug use 90% (DU90%) and adherence to hospital formulary were used as general qualitative indicators.[12,13]

METHODS

The Metropolitan Medical Center Hospital (MMCH) serves inpatients (169 beds) and outpatients (460 patients /day in average). The hospital formulary was first published in December 1999, and implemented in January 2000. The formulary is arranged by substance and brand name (including all dosage form). A number of 168 brands from 51 antibiotics (J01 code) were included in the hospital formulary without restriction.

Antibiotic use was monitored 1 year before (1999) and 1 year after (2000) the implementation of the hospital formulary. The use of antibiotics was measured as the number of defined daily doses (DDDs), expressed quantitatively as the number of DDDs per 100 bed days (DDDs/hbd) for inpatients and DDDs per 1000 patients per day (DDDs/tpd) for outpatients. DDDs for antibiotics (J01 code) listed in the anatomical-chemical-therapeutical (ATC) index with DDDs 2001 were used in this study.[14]

The data were collected from hospital pharmacy records using the centralized computer database. The inpatient data were based on drug usage per patient, related to prescriptions used both from inpatient hospital pharmacy stock and ward stock. The outpatient data were based on prescriptions purchased at the outpatient hospital pharmacy department. The total days of hospitalization and the number of outpatients were collected using the hospital administration centralized computer database. The number of prescriptions and the name of patients were collected from the outpatient pharmacy department database.

The number of each dosage form of antibiotic was converted into the number of DDDs. The overall use for each year for inpatients and outpatients were determined. Then DDDs/hbd and DDDs/tpd were calculated for each year. We then calculated the number of rugs that accounted for 90% of the total volume of DDDs, both for before and after implementation of hospital formulary. The antibiotic use that accounted for 90% of the use (DU90%) was analyzed each year for inpatients and outpatients. The DU90% was determined by substance and brand name based on the hospital formulary system. Within the DU90% segment, the proportion of group antibiotics and percentages were determined. The index of adherence in DU90% was calculated as the percentage of the number of antibiotics (in DDDs) that appear on the hospital formulary of the total antibiotic DU90% segment. The index of adherence was calculated for inpatients and outpatients only in the period after implementation of the hospital formulary.

Statistical comparison of overall antibiotic use was evaluated using the Wilcoxon rank sign test, where a p value of ≤ 0.05 was considered statistically significant.[15]

RESULTS

The overall antibiotics use in MMCH was 124.96 DDDs/hbd and 3.51 DDDs/tpd in 1999. After the implementation of a hospital formulary in 2000, the inpatient antibiotics use was significantly decreased by 23.1% to 96,13 DDDs/hbd (p = 0.03), but the overall outpatient antibiotic usage decreased insignificantly by 5.1%, to 3.33 DDD/tpd during 2000 (p = 0.58).

The number of antibiotics for inpatients found in DU 90% by substance name was 23 out of 53 (43.4%) in 1999 compared to 22 out of 52 (42,3 %) in 2000. A total of 194 brand names were prescribed for inpatients in 1999. Of these, 118 (60.8%) pharmaceutical products made up 90% of the total number of prescriptions. In 2000 DU90% by brand name was 122 out of 199 (61.3%).

The index of adherence to the formulary by substance and by brand name in the DU90% segment of inpatients was 100% and 94.3 %, respectively. The adherence to the formulary by substance and by brand name in the DU90% segment of outpatients was 100% and 90.5%, respectively (Table 1).

The profile of DU90% by substance name for inpatients is shown in Table 2. The pattern of DU90% changed slightly. Procain penicillin and azithromycin were not found in DU90% 2000, and on the contrary thiamphenicol appeared. The most commonly drug used was ciprofloxacin, not only in 1999 (19.9%) but also in 2000 (18.8.0 %). However, cephalosporins were the most widely used class of antibiotics 34.0% in 1999 and 40.6 % in 2000. The use of first generation cephalosporin (cefradin) was decreased by 1.2%. Countering this decrease, there was an increase of 4.8% of second generation (cefuroxime and cefotiam), a 3.5% increased of third generation (cefotaxime, ceftazidime, ceftriaxon, cefixime, cefetamet, cefoperazone) and 0.8% increased of fourth generation (cefepime) cephalosporin usage. Consequently, the overall use of cephalosporins was increased (Table 2).

The number of antibiotics on the list DU90% by substance name for outpatients were 15 out of 49 (30.6%) in 1999 and 17 out of 48 (35.4%) in 2000. DU90% by brand name was 119 out of 191 (62.3%) in 1999 and 100 out of 157 (63.7%) in 2000 (Table 1). The most common drug used in 1999 was amoxicillin (27.8%) and the most widely used class antibiotics was aminopenicillin (27.8%). The pattern changed in 2000, amoxicillin use was greatly decreased from 27.8% to 16.8%, while ciprofloxacin use was increased from 10.6% to 17.6%. Consequently, the most common antibiotic used in 2000 was ciprofloxacin and the widely used class of antibiotics was the quinolones. Additionally, great differences were seen in tetracyclines and macrolides usage. The use of tetracyclines decreased from 11.8% in 1999 to 4.1%, and macrolides usage increased from 1.8% to 5.8%. Cephalosporins use was moderately increased from 11.0% to 14.0% (Table 3).

Table 1. Quantitave and qualitative indicators of the antibiotics use for inpatients and outpatient before (1999) and after implementation (2000) of hospital formulary

	1999	2000
Inpatient		
DDDs/100 bed-days	125.58	96.57*
Number of substance name		
Total	53	52
DU90%	23	22
Percentage DU90% of total	43.4	42.3
Number of brand name		
Total	201	206
DU90%	118	122
Percentage DU90% of total	58.7	59.2
Index of adherence (%)		
By substance	-	100.0
By brand name	-	94.3
Outpatient		
DDDs/1000 patients/day	3.51	3.33**
Number of substance name		
Total	49	48
DU90%	15	17
Percentage DU90% of total	30.6	35.4
Number of brand name		
Total	191	157
DU90%	119	100
Percentage DU90% of total	62.3	63.7
Index of adherence (%)		
By substance	-	100.0
By brand name	-	90.5

*significant, P = 0.03
** not significant, P = 0.58

Table 2. The DU90% inpatient profile of antibiotic use in 1999 and 2000

Class and substance name	Number of brand name		Percentage of DDDs of total DDDs	
	1999	2000	1999	2000
Quinolones				
Ciprofloxacin	8	9	19.9	18.8
Ofloxacin	4	6	2.9	2.7
Fleroxacin	2	2	1.8	1.5
Levofloxacin	1	0	1.3	0.0
Cephalosporins				
Cefradin	6	9	11.5	10.3
Cefuroxime	8	8	5.8	7.3
Cefotiam	2	2	1.5	4.9
Cefotaxime	7	5	2.9	4.7
Ceftazidime	2	2	1.5	2.0
Ceftriaxon	4	5	3.9	3.0
Cefixime	3	2	2.5	2.5
Cefetamet	1	1	1.2	1.7
Cefoperazon	1	1	1.4	1.5
Cefepime	1	1	1.8	2.6
Aminopenicillins				
Amoxicillin	13	15	8.2	5.3
Ampicillin	14	12	2.7	3.0
Potentiated aminopenicillin				
Co-amoxiclav	13	13	5.4	5.2
Sultamicillin	2	2	2.4	4.1
Beta- lactamase sensitive penicillins				
Procain penicillin	1	0	3.1	0.0
Macrolides				
Azithromycin	5	0	4.2	0.0
Sulfonamides+Trimethoprim				
Co-trimoxazol	13	13	1.5	1.7
Tetracyclines				
Doxycycline	2	2	1.2	2.7
Aminoglycosides				
Gentamycin	5	5	1.0	1.1
Neomycin	1	1	0.0	1.9
Amphenicols				
Thiamphenicol	0	7	0.0	1.2
Total % of DDDS			89.7	89.8

The number of antibiotics in the DU90% segment was 22-23 for inpatients compared to 15-17 for outpatients. Great differences were seen in the cephalosporins use. In the DU90% segment for inpatients, 10 cephalosporins was found, compare to 5 cephalosporins counted in the DU90% segment for outpatients. Furthermore, the most frequent cephalosporin used for inpatients was the third generation cephalosporins, whereas the first generation cephalosporin was the most frequent cephalosporin used for outpatients. In the DU90% segment of inpatients, lincosamides (clindamycin and lincomycin) was not found, and, aminoglycosides (gentamycin and neomycin) was not found in the DU90% of outpatients.

Table 3. The DU90% outpatient profile of antibiotic use in 1999 and 2000

Class and substance name	Number of brand name		Percentage of DDDs of total DDDs	
	1999	2000	1999	2000
Aminopenicillin				
Amoxicillin	16	12	27.8	16.8
Tetracycline				
Doxycycline	3	2	11.8	4.1
Quinolones				
Ciprofloxacin	8	6	10.6	17.6
Ofloxacin	5	3	2.7	3.4
Sulfonamides+Trimethoprim				
Co-trimoxazol	14	14	6.7	6.3
Potentiated aminopenicillin				
Co-amoxiclav	10	8	5.4	8.4
Cephalosporins				
Cefradine	8	5	4.8	6.5
Cefadroxil	10	8	2.5	0.0
Cefuroxime	7	4	1.9	2.4
Cefixime	2	2	1.8	3.6
Cefalexin	0	2	0.0	1.5
Lincosamides				
Clindamycin	6	6	4.2	3.3
Lincomycin	7	4	2.3	3.1
Macrolides				
Azithromycin	7	4	3.4	4.6
Erythromycin	12	9	1.8	2.0
Roxithromycin	0	2	0.0	2.0
Spiramycin	0	3	0.0	1.8
Amphenicols				
Thiamphenicols	6	5	2.5	2.3
Total % of DDDs			90.2	89.7

DISCUSSION

Antimicrobial use is influenced by the interplay of knowledge, expectations and interactions of prescriber and patient, economic incentives, characteristics of the health system, and the regulatory environment.[1,2] The majority of prescribers and wider medical specialties in MMCH treating outpatients do not follow the formulary used by in treating inpatients. Therefore it was difficult to provide any effective control of compliance with hospital formulary by outpatient prescribers. Furthermore, the patient characteristics between in-patient and outpatients were considerably different. All these conditions were the reason why it would seem that antibiotic use was insignificantly decreased for outpatients.

Although considerably less effective than the restrictive method, the hospital formulary is widely used and still effective method to improve antimicrobial use.[1,7,8] The results of this study confirmed this finding, but the results was distinctly more successful in in-patients setting only.

The antibiotics prescribing rate in MMCH for inpatient was about 1 DDDs/patient /day which seems considerably similar to the Bouali teaching hospital, in Teheran, Iran.[16] However, in comparison with other hospitals in Europe, the use of antibiotics in MMCH was notably higher. At the University Hospital Center in Rijeka, Croatia antibiotics used in the first semester and second semester of 1997 were 45.9 DDDs/hbd and 32.9 DDDs/hbd.[17] The consumption of antibiotic at the University Teaching Hospital in Hradec Králové, Czech Republic, was 36.8 DDDs/hbd[18] and 42 DDDs/hbd at Olomouc Faculty Hospital (OFH), Czech Republic, in 1999.[19] At the San Martino Teaching Hospital (SMTH) Genoa, Italy antibiotic usage was 28.00 DDDs/ hbd during 1998.[20] Although with the ATC/DDD methodology suggested by WHO for drug use studies, comparisons between international centers can be performed, the comparisons must be interpreted cautiously with regards to several differences. The differences in the prevalence of diseases and resistance patterns, the availability of drugs, hospital and national regulations, the type and size of the hospitals, differences in time and duration of study, physician and patient characteristics can cause differences in the quantity of DDDs/hbd between countries.[11,16,21] The fact that MMCH is a private hospital and the fact that drugs taken home are recorded on the patients' records can cause overestimation.

Otherwise, the antibiotic use for outpatients in MMCH was lower than in Olomouc Faculty Hospital, Czech Republic was 6.4 DDDs/tpd.[18] This difference could be affected by the characteristic of patient coverage. In an outpatient setting of MMCH, a number of patients visited the skin and cosmetic clinic and the nutrition clinic are rarely prescribed a great number of antibiotics. Furthermore, there were also quite a number of pediatric patients, with doses substantially lower than the established DDDs. These factors could cause underestimation of antibiotic use in the outpatient setting.

Although ciprofloxacin is not recommended as the drug of first choice for lower respiratory tract infections, acute sinusitis and urinary tract infections, ciprofloxacin is the most potent fluoroquinolones against Pseudomonas aeruginosa.[22,23,24] Moreover it has some activity against Salmonella sp.[22] which causes frequent cases of infection in MMCH, without the aplastic anemia side-effect of chloramphenicol. These reasons could explain the high use of ciprofloxacin in MMCH. This result was different to studies in UHC Rijeka, Croatia. This was because ciprofloxacin was on the list of restricted antimicrobial agent in UHC Rijeka, which needed to reduce the risk of resistance development because of its relatively high cost.[17] Ciprofloxacin is one of several antibiotics commonly on the list of restricted antimicrobial use in several hospitals in USA.[8] Several studies indicated that pneumococci with reduced susceptibility to fluoroquinolones are now appearing in the USA.[25] The susceptibility of P aeruginosa to ciprofloxacin has declined over an 8-year period at a large university hospital.[26] Quinolon resistance monotherapy may worsen the increasing problem of antibiotic resistance in the nosocomial setting. Therefore, the high use of ciprofloxacin in MMCH requires special concern.

Cephalosporins were the most widely used class of antibiotic use for in-patients in 1999 and 2000. This result is similar to the study in SMTH Genoa, Italy and the study in Buoali Hospital, Iran.[16,20] The increased use of second and third generation cephalosporins for inpatients and outpatients (table 2 and table 3) can potentially lead to inappropriate use. Furthermore, the emergence and spread of extended spectrum beta lactamase-producing Klebsiella pneumoniae (ESBL-KP) are clearly promoted by widespread use of extended-spectrum cephalosporins, especially ceftazidime.[6] Thus, streamlining the number of third generation cephalosporin on the formulary should be considered.

Clindamycin is useful for mixed skin and soft tissue infection because of its activity against *Bacteroides fragilis*.[22] The high number patients of skin and cosmetic clinic resulted in clindamycin to be on the DU90% pattern for outpatient antibiotic use. The interchangeable use between macrolides and tetracycline on the DU 90% profile for outpatient antibiotic use before and after formulary implementation could be explained in part by the fact that doxycyline and macrolides have considerable similar activity against respiratory tract infection.[22] The reason for the change in DU90% profile of outpatient use is probably because of the change in antibiotic resistance in MMCH, and will need more studies.

The adherence to hospital formulary was high for in-patients and outpatients, but the reason is probably because of many antibiotics available for use. The list of available drugs in the hospital pharmacy (formulary) affected the pattern of use. Further streamlining of the antibiotic formulary may be possible, especially with regard to the many brand names available for use. For comparison between hospitals, there were 20 substance names of 30 dosages form of antimicrobials in Bouali, Tehran, Iran,[16] 36 substance names of antibiotics available in San Martino Genoa, Italy,[20] while in MMCH there were 51 substance names of 168 brand names available. However, the numerous brands available on the market also pose a problem.

The lack of data of hospital resistance pattern during the study maybe regarded to be a weakness of this study so we were unable to evaluate the prescribing profile to assure the right implementation for containment of antimicrobial resistance. The fact that DDD is based on average adult dose and not established for topical preparation was the limitation of this study. However, the use of relative instead of absolute unit of measurements (DDDs per 100 bed days for inpatients and DDDs per 1000 patients per day for outpatients instead of total DDDs) in comparison considerably reduce the limitation.

CONCLUSION

In spite of the successful implementation of the hospital formulary on the quantity in patient setting and adherence, limiting and restricting the number of antibiotics to the antibiotic resistance patterns in MMCH should be done in order to update the formulary.

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