UTILIZATION OF RESTRICTED ANTIBIOTICS IN A UNIVERSITY HOSPITAL IN THAILAND

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Abstract. Antibiotic resistance, a major negative consequence of antibiotic overuse, is an important problem worldwide. Various means have been used to control antibiotic usage including the use of an antibiotic order form (AOF), restricted antibiotic formularies and provision of educational information. The present study was designed to evaluate the use of antimicrobials in a 1,000-bed university hospital. Antimicrobial agents, likely to be abused namely ceftazidime, cefepime, cefoperazone/sulbactam, imipenem/cilastatin, meropenem, ciprofloxacin, netilmicin, vancomycin, azithromycin and clarithromycin, were selected for evaluation. A simple AOF with educational information was used as a mean to follow up the treatment. The investigator collected data from the filled AOF and the patient's charts of the Department of Internal Medicine from June to November 2000; all relevant data were assessed. The appropriateness of antibiotic use, assessed according to the criteria specified in the AOF, showed that 74% of these antibiotics were prescribed appropriately; this may prove the effectiveness of the system used in the present study. However, 348 of the 430 prescriptions (80.9%) were prescribed empirically at the initial stage for treatment of nosocomial infections in patients with serious conditions like pneumonia, sepsis and febrile neutropenia. Drugs that were frequently used empirically were ceftazidime (37.9%), imipenem/cilastatin or meropenem (19.3%), and cefoperazone/sulbactam (12.1%) respectively. Ceftazidime and imipenem/cilastatin or meropenem were also frequently used inappropriately among 111 prescriptions that were classified as an inappropriate prescribing. The most common misuses were prescriptions of the drug that did not follow the specified indications (70 prescriptions), no dosage adjustment in patients with renal impairment (39 prescriptions), improper dose (12 prescriptions) and improper dosing interval (9 prescriptions). The results suggested overuse of certain antibiotics remain to be an unsolved problem. Better monitoring and strict controlled use of the problematic antibiotics, *ie* ceftazidime, imipenem/cilastatin or meropenem and vancomycin are essential to promote rational drug use as well as to reduce the frequency of drug resistance.

INTRODUCTION

Antibiotic resistance is a worldwide health problem. This has been attributed mainly to the overuse and/or inappropriate use of antibiotics frequently reported in communities as well as in hospital settings. The proportion of inappropriate prescription varies, ranging from 28.4 to 91% of total prescriptions in some reports (Achong *et al*, 1977; Castle *et al*, 1977; Aswapokee *et al*, 1990; Jakrawatana, 1999; Suwangool *et al*, 1991; Udomthavornsuk *et al*, 1991; Samittipat, 2000). For example, extensive use of imipenem/cilastatin led to increased incidence of imipenem-resistant *Pseudomonas aeruginosa* (Rahal *et al*, 1998). One of the possible measures to reduce the incidence of resistance is to control antibiotic use, as has been reported in relation to the reduction of nosocomial cephalosporin-resistant *Klebsiella* infection following control of cephalosporin usage (Rahal *et al*, 1998). Various interventions to improve antibiotic prescribing have been implemented in many hospitals. These

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include formalized antibiotic guidelines, restrictive antimicrobial prescribing forms, provision of a computerized information system to guide antimicrobial selection, short-listed antibiotics in hospital formularies, etc (Dickerson *et al*, 2000). Among these means, the antibiotic order form (AOF) appeared to be a simple and efficient method of choice (Dunbin *et al*, 1981; Kowalsky *et al*, 1982; Echols and Kowalsky, 1984; Avorn *et al* 1988; Lipsy *et al*, 1993; Soumerai *et al*, 1993; Gyssens *et al*, 1997).

The antibiotics expenditure at Ramathibodi Hospital increased sharply during 1988 to 1991 and the major expenses were for parenteral and broad spectrum antibiotics (Sirinavin *et al*, 1998). The hospital Executive Board, together with the Antibiotic Committee, therefore strictly controlled the use of three antibiotics namely, imipenem, vancomycin, and parenteral ciprofloxacin by a system using an antibiotic order form during 1992-1996 which resulted in 22-29% reduction of drug expenditure. The hospital therefore saved 1.41-1.87 million baht in 1992-1994 (Sirinavin *et al*, 1998). When the restriction measure was not closely monitored and enforced, the expense of these drugs increased from 6.6 million baht in 1995 to 11.6 million baht in 1996 (Sirinavin *et al*, 1998). The prescribers were reminded to fill the AOF again during 1997-1999 but there was no enforcement or follow-up. Therefore the expenditure of antibiotics during 1997-1999 remained as high as 51-61 million baht. In 1999, the hospital spent 17.2 million baht for broad-spectrum and costly antibacterials including imipenem, meropenem, ceftazidime, cefoperazone/sulbactum, parenteral ciprofloxacin and vancomycin. The expense of these antibiotics was equivalent to 31.1% of total antimicrobials expenditure (55.3 million baht) (Suvanakool 2000, unpublished data). Despite of their high cost, these drugs have been prescribed extensively. The present study to evaluate the appropriateness of antibiotic use, was supported by the national drug policy which requires a report of Drug Use Evaluation (DUE) for a list of certain drugs. We selected antibiotics which are costly, frequently prescribed and listed in the national essential drug list, 1999. The present study used the special AOF as an intervention measure to improve the prescribing of these drugs.

MATERIALS AND METHODS

A descriptive, concurrent study was performed to identify the pattern of prescribing and to evaluate the appropriateness of antibiotic utilization.

Hospital setting and antibiotic policy

Ramathibodi Hospital, a 1,000-bed university hospital, providing referral and tertiary care, with approximately 30,000 admissions per year. Broad spectrum and costly antibiotics with high volume of use which are prone to be abused, namely ceftazidime, cefepime, cefoperazone/sulbactam, imipenem/cilastatin, meropenem, ciprofloxacin, netilmicin, vancomycin, azithromycin and clarithromycin were selected. The AOF was slightly modified from the former AOF that was designed by Sirinavin *et al* (1998) and has been used in Ramathibodi Hospital since 1992 in order to provide more informations and make it more easily to fill. This form was accepted by the Antibiotic Committee prior to use (Appendix). The prescribers were asked to complete the AOF for hospital pharmacists to dispense the drug. These forms were reviewed daily by infectious specialists. However, prescribing decision was handled by the physicians in charge of each patient.

Antibiotic audits

The investigators collected all of the filled AOF forms the Department of Internal Medicine, Ramathibodi Hospital during 1 June 2000 to 30 November 2000. The patient's charts and all relevant clinical data were reviewed within 72 hours of drug dispensing. They included underlying disease, site of infection, place where the infection was acquired, reasons for using the drug, suspected or known causative bacteria and microbiological investigation of each patient. The patients were followed from the first day to the third or fifth day of treatment when the microbiological results were available. The clinical progress notes of the attending physicians were used to evaluate the clinical outcome on the follow-up day.

Appropriateness of these restricted antibiotics was assessed according to the following criteria : Firstly, justification of antibiotic prescribing as stated in the AOF. For example, if ceftazidime was prescribed empirically for patients in whom infection caused by *P. aeruginosa* was suspected or proven, especially infection in neutropenic patients, or by *Burkholderia pseudomallei* (melioidosis); the prescription will be classified as an appropriate prescribing. If there was a documented infection with pathogens known to be susceptible to the prescribed drug, the use of such drug would be classified as appropriate and was prescribed specifically to treat the identified pathogen (Appendix). Secondly, appropriateness of dosage regimen which included route of administration, dosage, dosing interval as well as dosage adjustment in geriatrics, in patients with hepatic or renal function impairment. Thirdly, reevaluation of the empirical treatment when the microbiological and susceptibility data were obtained. Discontinuation, continuation, changing of antimicrobial or dosage regimens were recorded. Patients who were treated with the restricted antibiotics for less than 3 days were excluded from the study.

Definition

Multiple drug-resistant Gram-negative bacilli (MDR/GNB) were organisms which were proved resistant to amikacin and ceftazidime.

Statistical analysis

Data are analyzed by the SPSS/PC 9.0 for Windows. Frequency and/or percentage of each variable are determined, such as sites of infection, places where infection was acquired, reasons for using of the restricted antibiotics, microbiological results and appropriateness of antibiotic usage.

RESULTS

Demographic data and prescribing pattern

Four hundred and thirty AOFs were collected from the Department of Internal Medicine, Ramathibodi Hospital during a 6-month study period (June 1-November 30, 2000). These prescriptions were prescribed to 213 patients, age 15-93 years, mostly for treatment of nosocomial infections (82.1%). Each patient had one or more of the following underlying diseases: leukemia or lymphoma (134), diabetes mellitus (86), hypertension, ischemic heart disease and congestive heart failure (68), cerebrovascular diseases (47), renal disease (42), non-hematologic malignancy (33), chronic lung disease (19), AIDS (17), cirrhosis (13), systemic lupus erythematosus (13), pulmonary tuberculosis (6), and others (56). Serious conditions that were frequently treated with these antibiotics were pneumonia, sepsis and febrile neutropenia (Table 1). The most commonly prescribed antibiotics were ceftazidime (37.9%), imipenem/cilastatin or meropenem (19.3%), cefoperazone/sulbactam (12.1%), parenteral ciprofloxacin (11.4%) and vancomycin (8.1%) respectively (Table 2). It was also noted that other anti-infective drugs particularly amikacin (32.4%), antifungal agent (*ie* amphotericin B and fluconazole, 19.6%), and metronidazole (9.5%) (Table 3) were often prescribed concomittantly with these restricted antibiotics for treatment of mixed infections.

Most of these antibiotics were prescribed empirically at the initial stage of treatment (80.9%, 348 prescriptions), but when the pathogens were identified and the results of susceptibility testing were available, the treatments were changed accordingly which brought the number of specific use up to 34.2% and the extent of empirical use down to 65.8%.

Table 1
Sites of infection or conditions which the restricted antibiotics were prescribed.

Sites of infection or conditions	Number (%)
Pneumonia	139 (32.3)
Sepsis	103 (24.0)
Febrile neutropenia	82 (19.1)
UTI	39 (9.1)
Intra-abdominal	27 (6.3)
Skin and soft tissue	17 (4.0)
Bone and joint	7 (1.6)
CNS	3 (0.7)
Vascular line	1 (0.2)
Others	12 (2.8)

Table 2
Frequency prescription of antibiotics to be evaluated.

Antibiotics to be evaluated	Number (%)
Intravenous drugs	
Ceftazidime	163 (37.9)
Imipenem or meropenem	83 (19.3)
Cefoperazone/sulbactam	52 (12.1)
Ciprofloxacin IV	49 (11.4)
Vancomycin	35 (8.1)
Netilmicin	10 (2.3)
Cefepime	6 (1.4)
Oral drugs	
Clarithromycin	25 (5.8)
Azithromycin	4 (0.9)
Ciprofloxacin PO	3 (0.7)

Table 3
Frequency of prescription of other antimicrobials that were prescribed concurrently.

Antimicrobials concurrently prescribed	Number (%)
Amikacin	160 (32.4)
Antifungus	97 (19.6)
Metronidazole	47 (9.5)
Anti-TB[a]	34 (6.9)
Antiviral	27 (5.5)
Sulfamethoxazole/Trimethoprim	18 (3.6)
Cloxacillin	17 (3.4)
Amoxicillin/clavulanate	12 (2.4)
Ofloxacin	11 (2.2)
Ceftriaxone	10 (2.0)
Clindamycin	10 (2.0)
Gentamicin	7 (1.4)
Erythromycin	6 (1.2)
Pefloxacin	3 (0.6)
Penicillin	2 (0.4)
Ampicillin	2 (0.4)
Tetracycline	2 (0.4)
Cefoxitin	2 (0.4)
Other	18 (3.6)

[a]Isoniazid, ethambutal, rifampicin, streptomycin.

Table 4
Appropriateness of the restricted antibiotic usage.

Data	N=430 (100%)
1.Appropriate use	319 (74.2)
2.Inappropriate use	111 (25.8)
2.1 use of any antibiotic is not followed the stated criteria	70 (63.1)
2.2 improper dose	12 (10.8)
2.3 improper dosing interval	9 (8.1)
2.4 not adjusted dose in renal impairment	39 (35.1)

The microbiological study yielded relevant positive results in only 215 out of 430 specimens (50.0%). Organisms identified most frequently were Gram-negative bacilli, 19.1% of which were multiple drug-resistant (MDR/GNB) and methicillin-resistant *Staphylococcus aureus* (MRSA, 7.9%). The bacterial isolates detected were *P. aeruginosa* (31.2%), *Klebsiella pneumoniae* (12.1%), *Enterobacter* species (6.5%), *Escherichia coli* (7.4%), *Acinetobacter* species (7.4%), methicillin-susceptible *S. aureus* (MSSA) (4.2%), methicillin-susceptible coagulase negative staphylococci (3.7%) and others (20.0%).

Clinical specimen cultures yielded bacteria only in 132 of 348 episodes of suspected bacterial infection. Microorganisms isolated from specimens of 63 episodes were multiply drug-resistant and were susceptible only to the restricted drugs. However, there were 22 prescriptions, where antibiotics were changed according to the sensitivity data, and 4 prescriptions that the antibiotics were continued despite the microbiological results showing that the pathogens were resistant to the drugs being used. In seven cases, pathogens were susceptible to first or second generation of cephalosporins but patients were treated with ceftazidime which would indicate an overuse of this drug. Among cultured negative specimens (216/348 specimens or 62.1%), the antibiotics were continued in most cases (167 prescriptions), 74 of which were due to the clinical improvement. Other 93 prescriptions were not stopped even though no clinical improvement is obtained. There were only 49 prescriptions that antibiotics were discontinued.

Table 5
Reasons whereby antibiotic use were judged as an inappropriate.

Drug	2.1	2.2	2.3	2.4
Ceftazidime	25	5	5	9
Imipenem/cilastatin	11	-	2	2
Meropenem	9	4	1	5
Vancomycin	9	2	-	5
Cefoperazone/sulbactam	9	-	-	-
Ciprofloxacin IV	4	-	1	-
Cefepime	1	-	-	1
Netilmicin	1	1	-	-
Clarithromycin	1	-	-	-
Total	70	12	9	39

N.B 2.1 = use of any antibiotic is not followed the stated criteria.
2.2 = agreed with the choice of antibiotics but the dose was inappropriate.
2.3 = agreed with the choice of antibiotics but the dosing interval was inappropriate.
2.4 = agreed with the choice of antibiotics but the dose and/or the dosing interval was not adjusted in patients with renal impairment.

Evaluation of appropriateness

According to the criteria mentioned above, 319/430 (74.2%) prescriptions were appropriate. The 111 prescriptions (25.8%) were prescribed inappropriately. Prescribing the drug beyond the limited indication specified in the AOF appeared to be the major problem of inappropriate use (70 prescriptions, 63.1%) followed by no dosage adjustment in patients with renal impairment and larger than the recommended doses with a shorter or a longer dosing interval (39 prescriptions, 35.1%) (Table 4). Among ten antibiotics evaluated, ceftazidime (51/111 prescriptions) was most frequently prescribed inappropriately followed by imipenem/cilastatin or meropenem (27/111 prescriptions), vancomycin (15/111 prescriptions), cefoperazone/sulbactam (9/111 prescriptions), parenteral ciprofloxacin (5/111 prescriptions), netilmicin (2/111 prescriptions), cefepime (1/111 prescriptions) and clarithromycin (1/111 prescriptions) respectively. Ceftazidime was most frequently prescribed for treatment of infections not indicated in the AOF, *eg* infections caused by *K. pneumoniae, E.coli, Enterobacter* spp, and it was often used without adjustment of dose and/or dosing interval in patients with renal impairment (Table 5).

DISCUSSION

The present study of 10 restricted antibiotics prescribed at the Department of Internal Medicine in a university hospital, for a period of 6 months (June 1-November 30, 2000) indicated that these antibiotics were frequently prescribed empirically at the initial treatment (80.9% or 348/430 prescriptions). This is because most patients suffering from pneumonia, sepsis and febrile neutropenia were in critical conditions which required an urgent treatment together with the clinical experiences of the prescribers which often faced with a problem of multiple drug resistant pathogens. The decision to use intravenous antibiotics for treatment of a suspected bacterial infection is usually made when the risk/benefit ratio favors early treatment. Moreover, a high incidence of multiple drug-resistant Gram-negative bacilli (19.1%) together with 7.9% of MRSA which were identified from the specimens would further support the need of a broad-spectrum antibiotics. When the pathogens were identified and the sensitivity results were available, some of the treatments (35/348 prescriptions) were reconsidered and antimicribials were changed accordingly. This brings the rate of empirical use

of antibiotics down from 80.9% to 65.8%. However, these antibiotics were continued in most cases (77.3% or 167/216 prescriptions) because of clinical improvement although no pathogen could be demonstrated or pathogens were not susceptible to the drugs being used. Such a high proportion of using antibiotics without evidence of infection can be explained partly by the high incidence of febrile neutropenia among these patients (28.2% or 61/216 prescriptions) which is the accepted criterion for prescribing antibiotics empirically in our study. Thus, the percentage of prescribing antibiotics inappropriately without documented evidence of infection will be lower from 77.3% to 49.1% which is lower than an earlier report in community hospitals elsewhere (62% in 7 community hospitals) (Scheckler and Bennet, 1970). This is similar to a recent study which reported 49% prescribing of antibiotics empirically for patients with no evidence of infection (Ehrenkranz *et al*, 1993). However, there was a report in which only 10% of hospitalized patients were treated with intravenous antibiotics empirically without evidence of infection at the Veterans Affairs Medical Center, Louisville, Kentucky (Ahkee *et al*, 1996) where there was a program to improve antibiotic use.

Our study is also an attempt to improve antibiotic prescribing and we monitored not only the intravenous antibiotics but also three oral antibiotics, namely clarithromycin azithromycin and ciprofloxacin. There were 13 prescriptions of these 3 oral antibiotics prescribed mainly for treatment of community-acquired pneumonia (11 clarithromycin, 1 azithromycin and 1 ciprofloxacin).

The present finding of high rate of appropriate use of these antibiotics (74.2%) may indicate the effectiveness of the AOF as well as the cooperation of all health personnel, the better follow-up system and of course the support of the policy makers. Since there were reports of high inappropriate use of antibiotics in teaching hospitals in Thailand ranging from 40-91% (Holloway, 2000). This is consistent with the finding of Suwangool *et al* (1991) who reported that a selective restriction policy of antibiotic use with the aid of agreed guidelines can lower the rate of inappropriate use of antibiotics from 32.8% to 18.8%. Similarly, Thuong *et al* (2000) demonstrated that using an antibiotic order form for restricted antibiotics and audited by pharmacists resulted in a more appropriate use of the antibiotics evaluated. However, Aswapokee *et al* (1992) reported a failure of improving antibiotic prescribing by using the AOF alone. Thus, prescribing guideline and close monitoring and cooperation of all hospital personnel are essential and indispensable from the AOF.

The 33.0% (142/430 prescriptions) of intravenous antibiotics were prescribed empirically without documented evidence of infection in our study which is still higher than one would expect since closed monitoring were performed (Ahkee *et al*, 1996). There were 111 out of 430 prescriptions (25.8%) assessed according to the stated criteria that antibiotics were used inappropriately. This is similar to the report of Ahkee *et al* (1996) who reported that one of the common reasons for prescribing antibiotics inappropriately is giving them to patients without documented infection. Ceftazidime was also most frequently prescribed empirically because of its excellent activity against a wide spectrum of Gram negative bacteria, especially *P. aeruginosa* (USPDI, 2000). This may be attributed to our very limited indication of ceftazidime (use only for *P. aeruginosa* infection and melioidosis). In addition, ceftazidime was found to be used inappropriately because its dosage adjustment was not done in patients with renal impairment. Thus, educational program for prescribers should be beneficial.

The present results indicated that all 10 antibiotics evaluated were used appropriately in a majority of cases (74.2%), although they were often prescribed empirically at the initial stage of treatment (80.9%). This may be attributed partly to the fact that patients who are admitted to a tertiary care hospital are those with a serious condition, and partly to the high incidence of nosocomial infection. Among 10 antibiotics evaluated, ceftazidime was most frequently abused.

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Appendix antibiotic order form

Antibiotic order form
(in-patient)

1. **Ward**.....
2. **H.N.**..... Patient's name..... Age.....

3. **Underlying disease** ☐ Yes, specified.....
   ☐ No
4. **Sites of infection or conditions for which this drug was prescribed**
   - ☐ Bone and joint
   - ☐ CNS
   - ☐ Febrile neutropenia
   - ☐ Intra-abdominal
   - ☐ Pneumonia
   - ☐ Sepsis
   - ☐ Skin & soft tissue
   - ☐ UTI
   - ☐ Vascular line
   - ☐ Others, specify .....
5. **Place where infection was acquired**
   - ☐ Community
   - ☐ Other hospital
   - ☐ This hospital
6. **Reson for use**
   - 6.1 ☐ **Empirical therapy** (*ie* site and / or pathogen unknown)
   - 6.2 ☐ **Specific therapy** (*ie* site and pathogen known based on culture sesult)

Was Gram stain of appropriate clinical specimen performed?
☐ No ☐ Yes, specified .....

Was a culture sent prior to the initiation of therapy?
☐ No, because .....
☐ Yes; ☐ Blood ☐ CSF ☐ Sputum ☐ Urine
☐ Wound ☐ Medical device .....
☐ Others.....
Suspected pathogens.....

Microbiological result ☐ MRSA or MRSE ☐ MDR-GNB ☐ NOT MDR
- ☐ *Staph. aureus.*
- ☐ *Pseudo. aeruginosa*
- ☐ *Kleb. pneumoniae*
- ☐ *Enterobacter* spp
- ☐ *E. coli*
- ☐ *Acinetoabcter* spp
- ☐ Others.....

Prescribed antibiotics
(Should consult infectious disease specialist before prescribing)

Start date.....
Reason for not using other antibiotics.....
.....

Drug name	Criteria for use
PARENTERAL DRUGS	
☐ Ceftazidime	Infection caused by *Pseudomonas aeruginosa* and melioidosis
☐ Ciprofloxacin	Infection caused by multiple drug resistant gram-negative bacteria
☐ Imipenem	Infection of multiple drug resistant gram-negative bacteria and susceptible only to this drug
☐ Meropenem	Same as that for imipenem
☐ Netilmicin	Infection of gram-negative bacteria which resist to gentamicin and amikacin and susceptible to this drug
☐ Sulperazone	Infection caused by *Acinetobacter* spp. and/or infection of multiple drug resistant gram-negative bacteria and susceptible to this drug
☐ Vancomycin	Infection caused by gram-positive resistant to all other drugs such as MRSA and MRSE
☐ Cefepime	Infection caused by multiple drug resistant gram-negative bacteria
ORAL DRUGS	
☐ Azithromycin	Prevention of infection caused by Nontuberculosis mycobacteria in AIDS
☐ Ciproflozacin	Infection of multiple drug resistant gram-negative bacteria and/or mild infection caused by *Pseudomonas aeruginosa*
☐ Clarithromycin	Infection caused by Nontuberculosis mycobacteria and/or *H. pylori*

● Physician who prescribed name..... Code .....
○ Phycician who filled this form name..... Code .....

(Please complete all 2 pages)