ASSESSMENT OF APPROPRIATENESS OF RESTRICTED ANTIBIOTIC USE IN CHAROENKRUNG PRACHARAK HOSPITAL, A TERTIARY CARE HOSPITAL IN BANGKOK, THAILAND

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Abstract. The purpose of this study was to evaluate the appropriate of restricted antibiotics at a tertiary care hospital in Bangkok, Thailand. Data from patient charts during September-November, 2009 were obtained regarding appropriate use of antibiotics following hospital antibiotic guidelines. Of 307 prescriptions reviewed, the prevalence of appropriate antibiotic use was 74.6% (229/307). Most patients were male (185/307) with a mean age of 64.2±18.0 years. There was a significant association between appropriate antibiotic use and patients having underlying disease, a previous history of recent antibiotic use, a recent hospitalization, admission to a medical unit and having a recent health-care institution acquired infection ($p<0.001$). The diagnosis of pneumonia was associated with proper use of antibiotics compared with other diagnoses (OR 1.8). Admission to a medical ward was more likely to be associated with correct antibiotic use than having surgery (OR 7.8 and 0.07). Having a health-care institution acquired infection more likely to be associated with appropriate antibiotic use than having a community acquired infection (OR 5.5 and 0.13). Meropenem was more likely to be used appropriately than cefoperazone/sulbactam (OR 1.9 and 0.2). After multivariate analysis, controlling confounding factors, admission to a medical unit and having a health-care institution acquired infection were factors associated with proper use of restricted antibiotics (adjusted OR 9.0 and 7.1; 95% CI 2.27-35.73 and 2.38-20.95; $p=0.002$ and $p<0.001$, respectively). The prevalence of appropriate use of restricted antibiotics was high; physicians followed local hospital antibiotic guidelines. Future studies of compliance with hospital antibiotic guidelines and its impact on bacterial resistance and infection related mortality should be carried out to determine if appropriate antimicrobial use leads to improve outcomes.

Keywords: restricted antibiotic use, tertiary care hospital, Thailand

INTRODUCTION

The emergence of worldwide antibiotic resistance is a major public health problem, impacting patient treatment and outcomes. Antibiotic resistance continues to increase among bacteria that cause community and hospital acquired infections (Whitney *et al*, 2000; Fridkin *et al*, 2001, 2002; Neuhauser *et al*, 2003).

The development of antibiotic resis-

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tant organisms is related to overuse and/or inappropriate use of antibiotics, especially in developing countries where antibiotics can be purchased without prescription and broad spectrum antibiotics can be prescribed by any clinician (Thamlikitkul *et al*, 1998). In Thailand, inappropriate prescriptions comprise 24.8 to 91.0% of total prescriptions (Aswapokee *et al*, 1990; Udomthavornsuk *et al*, 1990; Thamlikitkul *et al*, 1998; Apisarnthanarak *et al*, 2006b). Various interventions to improve antibiotic prescribing have been implemented in many hospitals. These include formalized antibiotic guidelines, restricting antimicrobial prescribing, provision of a computerized information system to guide antibiotic selection and short-listed antibiotics in hospital formularies (Dickerson *et al*, 2000).

The antibiotic use at Charoenkrung Pracharak Hospital increased sharply during 2004-2007. The majority of antibiotics prescribed were parenteral and broad spectrum. There is also increasing antibiotic resistance, especially *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, ESBL-producing *Eschelicia coli, Klebsiella pneumoniae* and methicillin resistant *Staphylococcus aureus*. At this hospital, broad-spectrum antibiotics that tend to be inappropriately used are: piperacillin/tazobactam, cefoperazone/sulbactam, imipenem/cilastatin, meropenem and vancomycin. The Infectious Control Committee at this hospital and the Drug Utilization Evaluation Committee surveyed appropriate use of these restricted antibiotics during 1 January 2008 - 28 February 2008. The appropriate use of restricted antibiotics was only 57.8%. Cefoperazone/sulbactam, piperacillin/tazobactam and meropenem were inappropriately used 25.0, 19.4 and 16.7% of the time, respectively.

MATERIALS AND METHODS

A study was carried out to assess the appropriateness of restricted antibiotic use after implementation of local hospital antibiotic guidelines at Charoenkrung Pracharak Hospital, a 410-bed tertiary level hospital in Bangkok, Thailand. This hospital has approximately 25,000 admissions per year, antibiotics are prescribed by each physician. There are 2 infectious diseases specialists (one for adults and one for pediatrics) who evaluate patients with infectious diseases on a consultation basis. Antibiotic resistance is conveyed to all physicians through a hospital antibiogram every 6 months. The antibiotics on restricted use are told to the physicians.

Definitions

The criteria used to define the need for antimicrobial therapy were adopted from the current edition of Principles and Practices of Infectious Disease (Mandel *et al*, 2005). We used local hospital antibiotic guidelines developed from existing published guidelines to determine appropriateness of antibiotic use. The antibiotic guidelines were prepared by the 2 infectious diseases specialists, modified and agreed to by all physicians and approved for use by the infectious control committee as guidelines for clinical practice at Charoenkrung Pracharak Hospital. The guidelines included a short description of all antibiotics available at Charoenkrung Pracharak Hospital, the recommended dosage for each antibiotic, the principles of antibiotic use for prophylaxis and treatment of infectious diseases, antibiotics recommended for prophylaxis, and antibiotics recommended for treatment of known or suspected organisms. Modifications were made to accommodate local susceptibility patterns of nosocomial pathogens.

Program design

The local hospital antibiotic guidelines had been implemented since August 2008.

This prospective study was carried out during 1 September 2009-30 November 2009. We evaluated physician compliance to hospital antibiotic guidelines. All hospitalized patients receiving restricted antibiotics, piperacillin/tazobactam, cefoperazone/sulbactam, imipenem/cilastatin, meropenem and vancomycin, were included in the study. Each patient included in the study was visited 3 times: 1) on enrollment in the study, to document empiric use of antibiotics; 2) 72 hours after enrollment, when microbiologic results were available; and 3) on the day of discharge, when the final diagnosis was given. Data collected were patient demographics history of underlying disease, the hospital unit, site of infection, where the infection was acquired, reasons for using the antibiotic, suspected or known causative bacteria, microbiological investigation results, appropriateness of antibiotic used and route of administration, dosage and dosing interval of the antibiotic, along with any dosage adjustment for geriatrics or for patients with hepatic or renal impairment. Appropriateness of the antibiotic was assessed using the following criteria: 1) justification of antibiotic prescribing as directed by hospital antibiotic guidelines; for example, if cefoperazone/sulbactam was prescribed empirically for a patient in whom the infection was caused by *A.baumanii* was suspected or proven, the prescription was classified as appropriate prescribing; 2) appropriateness of dosage regimen, which included route of administration, dosage, dosing interval and dosage adjustment for geriatrics or in patients with hepatic or renal impairment; 3) reevaluation of empiric treatment when the microbiological and susceptibility data were obtained. Discontinuation, continuation, changing of antimicrobial or dosage regimens were also recorded. Patients treated for fewer than 3 days were excluded from the study. All data were collected by one investigator who was blinded to the prescriber and patient identification data. Prescribing physicians were unaware of the purpose of the study at the time of chart review.

Statistical analysis

Data are analyzed by the Strata program. Frequency and/or percentage of each variable were determined, such as site of infection, place where the infection was acquired, reason for using restricted antibiotics and appropriateness of antibiotic use.

Categorical variables were compared using the chi-square test or Fisher exact test where appropriate and continuous variables were compared using the Mann-Whitney *U* test. All tests were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

Demographic data and prescribing patterns

During the 3-month study period (1 September 2009-30 November 2009), 307 prescriptions for restricted antibiotics were written for 273 patients, aged 15-96 years. The number of prescriptions written by internal medicine, surgery and orthopedic physicians were 269, 31 and 7, respectively. Most of the prescriptions were written for hospital acquired or health-care institution associated infections (79.5%). Two hundred seventy-two prescriptions (88.6%) were written for empiric treatment. Each patient had at least one of the following underlying diseases: cardiac disease, diabetes mellitus, cerebro-

vascular disease, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, cirrhosis and AIDS. Frequently treated conditions included sepsis and pneumonia (Table 1).

The most commonly prescribed antibiotics were piperacillin/tazobactam (36.5%), meropenem (31.9%), vancomycin (12.1%), cefoperazone/sulbactam (10.1%) and imipenem/cilastatin (9.4%).

The most frequently identified organisms in sepsis and urosepsis were ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae;* whereas *Acinetobacter baumanii* and *Pseudomonas aeruginosa* were the most commonly found organisms in pneumonia cases.

Evaluation of appropriateness

Two hundred twenty-nine of 307 prescriptions (74.6%) were prescribed appropriately per hospital antibiotic guidelines. In 78 patients (25.4%) antibiotics were inappropriately prescribed. Prescription of outside its indications as specified by hospital antibiotic guidelines was the major inappropriate use (66/307, 21.4%) (Table 2).

Table 1
Sites of infection or conditions for which restricted antibiotics were prescribed (*N*= 307).

Site of infection or conditions	Number (%)
Severe sepsis	114 (37.1)
Pneumonia	107 (34.9)
Urosepsis	38 (12.4)
Gastrointestinal tract infection	25 (8.1)
Other [a]	23 (7.5)

[a] Skin and skin structure infection in 15 (4.9%), bone and joint infection in 5 (1.6%) and central nervous system infection in 3 (1.0%).

Table 2
Appropriateness of restricted antibiotic use (*N*=307).

Data	Number (%)
Appropriate use	229 (74.6)
Inappropriate use	78 (25.4)
Use of an inappropriate antibiotic	66 (21.4)
Use of an inappropriate dose	6 (2.0)
Use of an inappropriate dosing interval	6 (2.0)

Table 3
Reason the antibiotic used was judged as inappropriate.

Drug	Antibiotic[a]	Dose[b]	Interval[c]
Cefoperazone/sulbactam	14	1	4
Imipenem/cilastatin	6	1	1
Piperacillin/tazobactam	26	3	0
Meropenem	16	1	0
Vancomycin	4	0	1
Total	66	6	6

[a]Use of antibiotic did not follow guidelines.
[b]Appropriate choice of antibiotics but dose inappropriate.
[c]Appropriate choice of antibiotic but dosing interval inappropriate.

Of the 5 antibiotics evaluated, cefoperazone/sulbactam (19/31, 61.3%) was the most inappropriately prescribed antibiotic, followed by imipenem/cilastatin (8/29, 27.6%), piperacillin/tazobactam (29/112, 25.9%), meropenem (17/98, 17.4%) and vancomycin (5/37, 13.5%). The reason the antibiotic used was judged as inappropriate are summarized in Table 3.

A comparison of characteristics between patients receiving appropriate and inappropriate antibiotics is summarized in Table 4.

On univariate analysis, patients with underlying diseases, who previously received antibiotics or who were recently hospitalized were associated with more appropriate antibiotic use [odds ratio (OR), 10.2, 7.7 and 5.3; 95 % confidence intervals (CI), 2.9-44.5, 3.8-15.6 and 2.8-9.9, respectively]. Pneumonia was associated with appropriate antibiotic use (OR 1.8; 95% CI 1.0-3.3). Gastrointestinal tract infection had a lower incidence of appropriate antibiotic use (OR 0.19; 95% CI 0.07-0.49). Admission to the medicine department was associated with more appropriate antibiotic use (OR 7.8; 95% CI 3.6-17.7). Admission to the surgery department was associated with a lower incidence of appropriate usage (OR 0.07; 95% CI 0.03-0.18). Health-care associated infections were associated with more appropriate antibiotic use (OR 5.5; 95% CI 2.6-12.5). Community acquired infection was associated with a lower incidence of appropriate antibiotic use (OR 0.13; 95% CI 0.07-0.25). Meropenem was associated with appropriate antibiotic use (OR 1.9; 95% CI 1.05-3.82). Cefoperazone/sulbactam was associated with a lower incidence of appropriate antibiotic use (OR 0.2; 95% CI 0.07-0.40). There were no differences in other characteristics or risk factors between those who received appropriate antibiotics and those who received inappropriate antibiotics (Table 4).

On multivariate analysis, after controlling for confounding factors, admission to the medicine unit and having health-care associated infection were factors related to the proper use of restricted antibiotics (adjusted OR 9.0 and 7.1; 95% CI 2.27-35.73 and 2.38-20.95; p=0.002 and <0.001, respectively).

DISCUSSION

We evaluated the appropriate use of restricted antibiotics, following hospital antibiotic guidelines, using a prospective audit of prescriptions. Five antibiotics studied were: piperacillin/tazobactam (112 prescriptions), meropenem (98 prescriptions), vancomycin (37 prescriptions), cefoperazone/sulbactam (31 prescriptions) and imipenem/cilastatin (29 prescriptions). The justification for and appropriateness of the antibiotic used, reassessment of the therapy and duration of treatment were determined and compared with hospital antibiotic guidelines. Most of the antibiotics (88.6%, 272/307) were prescribed empirically for initial treatment. Most of the patients had severe sepsis, pneumonia or urosepsis; these are critical conditions requiring urgent treatment, based on the clinical experience of the prescriber who may be faced with multiple antibiotic resistant organisms.

This study shows implementation of hospital antibiotic guidelines may be associated with a reduction in inappropriate restricted antibiotic use from 42.2% to 25.4%. These findings are consistent with those of Suwangool *et al* (1991) who found a restrictive policy of antibiotic use with agreed upon guidelines can lower the rate of inappropriate antibiotic use from 32.8% to 18.8%. In this study, the incidence of

Table 4
Comparison of characteristics between patients receiving appropriate and inappropriate antibiotics.

Characteristics	Patient in entire cohort (*N*=307)	Patient receiving appropriate antibiotics (*N*=229)	Patient receiving inappropriate antibiotics (*N*=78)	*p*-value
Median age in years (range)	71 (15-90)	70 (15-96)	69 (19-93)[a]	NS
Male sex	185 (60)	148 (65)	37 (47)	0.007[e]
Underlying disease	291 (95)	225 (98)	66 (85)[b]	<0.001[e]
Previous antibiotics	256 (83)	210 (92)	46 (59)[b]	<0.001[e]
Previous hospitalization	246 (80)	201 (88)	45 (58)[b]	<0.001[e]
Type of disease				
Severe sepsis	114 (37)	92 (40)	22 (28)[b]	NS
Pneumonia	107 (35)	87 (38)	20 (26)[b]	0.005[e]
Urosepsis	38 (12)	29 (13)	9 (12)[b]	NS
Gastrointestinal tract infection	25 (8)	10 (4)	15 (19)[b]	<0.001[e]
Others[d]	23 (8)	11 (5)	12 (15)	0.002[e]
Admission ward				
Surgery	31 (10)	7 (3)	24 (31)[b]	<0.001[e]
Medicine	269 (88)	216 (94)	53 (68)[b]	<0.001[e]
Orthopedic	7 (2)	6 (3)	1 (1)[c]	NS
Place of disease contracted				
Community	63 (21)	25 (11)	38 (49)[b]	<0.001[e]
Hopital	132 (43)	102 (45)	30 (39)[b]	NS
Health-care institution	112 (37)	102 (45)	10 (13)[b]	<0.001[e]
Drug				
Cefoperazone/sulbactam	31 (10)	12 (5)	19 (24)[b]	<0.001[e]
Piperacillin/tazobactam	112 (37)	83 (36)	29 (37)[b]	NS
Meronem	98 (32)	81 (35)	17 (22)[b]	0.026[f]
Imipenem/cilastatin	29 (10)	21 (9)	8 (10)[b]	NS
Vancomycin	37 (12)	32 (14)	5 (6)[b]	NS
Reason for use				
Specific	35 (11)	24 (11)	11 (14)[b]	NS
Empiric	272 (89)	205 (89)	67 (86)[b]	NS

NOTE, Data are no. (%) of patients.
[a]Mann-Whitney *U* test; [b]Chi-square test; [c]Fisher's exact test; [d]Skin and skin structure infection, bone and joint infection, and central nervous system infection; [e]Highly significant; [f]significant
NS, Not significant

inappropriate antibiotic use was 25.4% (78/307 prescriptions), with the main reason being lack of indication for antibiotic use according to hospital antibiotic guidelines. In Thailand, the proportion of inappropriate prescription varies, ranging from 24.8% to 91.0% of total prescriptions (Aswapokee *et al*, 1990; Udomthavornsuk *et al*, 1990; Thamlikitkul *et al*, 1998; Apisarnthanarak *et al*, 2006b). Aswapokee *et al* (1990) reported a 91% incidence of inappropriate antibiotic use among

Table 5
Incidence and patterns of inappropriate antibiotic use (IAU) at a tertiary care hospital in Thailand.

Reference	Type of study	No. of patients	Patients receiving antibiotics, %	Incidence of IAU, %	Reasons for IAU
Udomthavornsuk *et al*, 1990	Incidence[a]	400	NA	52.3	Inappropriate surgical prophylaxis[b], no indication for use, or redundant antibiotic spectrum.
Aswapokee *et al*, 1990	Prevalence	690	44	91	No indication for use, inappropriate choice of antibiotic or inappropriate dose, interval or duration.
Thamlikitkul *et al*, 1998	Prevalence	29,929	41[c] and 19[d]	50	Inappropriate surgical prophylaxis[b], inappropriate antibiotic for normal labor, inappropriate antibiotic for cataract surgery, inappropriate antibiotic for acute diarrhea, or inappropriate antibiotic for respiratory tract infection.
Apisarnthanarak *et al*, 2006b	Prevalence	502	63.5	24.8	No indication for use, inappropriate surgical prophylaxis[b], inappropriate antibiotic for resistant microorganisms, use of broad-spectrum antibiotics where a narrow spectrum antibiotic is available and effective or other reasons[e].
Present study	Prevalence	1,200	23[f]	25.4	Use of any antibiotic not following guidelines, inappropriate dose or dosing interval.

NA, Not applicable
[a]This was a prospective study to evaluate all antibiotic prescriptions written for 1 month.
[b]For inpatients; [c]For outpatients; [d]Includes choice of antibiotic, dose, interval, and duration.
[e]Includes choice of inappropriate antibiotic, administration of antibiotic with a redundant spectrum, an inappropriate dose, interval, duration, and administration of antibiotics to colonized patients.
[f]Patients receiving restricted antibiotics

medical units of a tertiary care university hospital in Bangkok, mainly due to antibiotic use without evidence of infection. Udomthavornsak *et al* (1990) reported the incidence of inappropriate antibiotic use of 52.3% at a tertiary care university hospital in northeastern Thailand. In our study, the incidence of inappropriate use of antibiotics was 42.3% among patients who received empiric therapy (because of a lack of an indication for antibiotic use), 82.4% among patients who received surgical prophylaxis (mainly as a result of delayed use and excessive duration of >72 hours), and 39.6% among patients with a documented infection (mainly as a result of inappropriate antibiotic choice and using antibiotics with a redundant spectrum). Thamlikitkul *et al* (1998) reported the incidence of inappropriate antibiotic use was 50% among inpatients and outpatients at a tertiary care university hospital in Bangkok. Inappropriate antibiotic choices, duration of surgical prophylaxis, and use of antibiotics for acute diarrhea and for upper respiratory tract infections were the main reasons found for inappropriate use of antibiotics. Apisarnthanarak *et al* (2006) reported the incidence of inappropriate antibiotic use was 24.8% among inpatients at a tertiary care university hospital in Bangkok. No indication for use, inappropriate use for surgical prophylaxis, inappropriate antibiotics for resistant organisms and use of broad-spectrum antibiotics where a narrow spectrum antibiotic was available and effective, were the main reason for inappropriate use of antibiotics.

Variations in the incidence of inappropriate antibiotic use may be the result of different study designs, patient demographic characteristics, and definitions of inappropriate use of antibiotics among published studies. Data regarding incidences and patterns of inappropriate antibiotic use (IAU) in tertiary care hospitals in Thailand are summarized in Table 5.

Improving antibiotic use in hospitals is a challenging task that raises complex issues (McGowan, 1994; Goldmann *et al*, 1996; Kollef *et al*, 1997). Many methods have been proposed to control antibiotic use in hospitals, such as educational programs, development of a restrictive hospital formulary, reports of sensitivity results, regulations regarding interactions between pharmaceutical representatives and physicians, controlled distribution, automatic stop-orders and written justification for specific antibiotics and /or requirement for expert approval before or after prescribing some drugs have been suggested (Kunin, 1978; Goldmann *et al*, 1996; John and Fishman, 1997; White *et al*, 1997). A combination of both restrictive and educational measures appears to be necessary to improve overall antibiotic use in hospitals (Moleski and Andriole, 1986; Avorn *et al*, 1987; White *et al*, 1997). It is often difficult to know which interventions has improved correct antibiotic use since several steps are often taken simultaneously (McGowan,1983).

There were several limitations with this study. The data from patients who received restricted antibiotics for less than 3 days were excluded from the study to prevent incomplete assessment; these may have fallen into either the appropriate or inappropriate use groups. Quasi experimental studies are susceptible to biases, especially concerning secular trends unrelated to the intervention. The challenging issue is how the results achieved with our study can be sustained, since each year there are new staff who prescribe antibiotics. Educational programs comprised of information feedback and antibiotic guidelines need to be revised every few

years with update information regarding the epidemiology of infectious diseases in Thailand and new antibiotics that become available should be controlled. Similar studies will be repeated periodically to determine if the effect is sustained and surveillance programs may focus on high-risk areas, such as intensive care units. The high rate of appropriate use of restricted antibiotics (74.6% or 229/307) indicates the initial effectiveness of the antibiotic policy and the cooperation of the physicians. Future studies of compliance with guideline recommendations and their impact on bacterial resistance and infection related mortality should be carried out to determine if the theory optimal antimicrobial use leads to a better quality of care is indeed supported by the data.

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