Implementation of Clinical Practice Policy on the Continuous Intravenous Administration of Amphotericin B Deoxycholate

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Background: *Systemic fungal infections have significantly increased. The mainstay of treatment is amphotericin B deoxycholate. A limitation of using amphotericin B includes infusion-related reactions and nephrotoxicity. A continuous infusion of amphotericin B was found to reduce nephrotoxicity and infusion-related reactions.*
Objective: *To implement clinical practice policy on the continuous intravenous administration of amphotericin B in the patients hospitalized in general medical wards at Siriraj Hospital.*
Method: *A one-page evidence-based clinical practice policy on continuous intravenous administration of amphotericin B was prepared and disseminated to all general medical wards in Siriraj Hospital. The information on the patients who received amphotericin B treatment between March 2004 and March 2006 was collected. The data were analyzed using descriptive statistics, univariate analysis and multiv ariate analysis as appropriate. A p-value of < 0.05 was considered statistically significant.*
Results: *Of 166 courses of amphotericin B treatment in 148 patients, 102 courses (61.4%) were given continuous intravenous administration of amphotericin B (CI group) and 64 courses (38.6%) were given conventional 4-to 6-hour intravenous administration (RI group). The mean age of the patients in the CI group was significantly greater than that in the RI group. The CI group had more patients with neutropenia with persistent fever whereas the RI group had more patients with HIV/AIDS and cryptococcal meningitis. The incidence of amphotericin B-related nephrotoxicity was 27.5% in the CI group compared with 39.1% in the RI group ($p=0.164$). Chills were observed in 6.9% of the patients in the CI group compared with 26.6% in the RI group ($p=0.001$). Overall mortality at the end of therapy was significantly higher in the CI group. However, most of the deaths in the CI group were unrelated to fungal infections or amphotericin administration.*
Conclusion : *Continuous infusion of amphotericin B was associated with a decrease in infusion-related reactions and tended to have less nephrotoxicity than those in the 4-to 6-hour infusion group.*

Keywords : *Continuous-infusion, Amphotericin B, Nephrotoxicity, Infusion-related reactions*

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Systemic fungal infections have significantly increased over the past 30 years[1-4]. Systemic opportunistic fungal infections constitute a leading cause of morbidity and mortality in neutropenic patients[5]. In addition, HIV-infected patients often have a variety of fungal infections, especially those who have CD4+ T lymphocyte counts of <50 cells/μL[6,7]. The common causative agents in HIV-infected patients include *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Penicillium maneffei* [8].

The mainstay of treatment for these patients is amphotericin B deoxycholate despite it being associated with significant drug-related adverse effects, especially infusion-related reactions, [9-11] and nephrotoxicity [12,13]. Over the past few years, several randomized trials revealed different strategies to reduce AmB-induced renal toxicity. These strategies included sodium supplementation,[14,15] concurrent administration of low-dose dopamine,[16] correction of potassium depletion[17] and slow infusion rates. Many recent

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clinical trials of new antifungal agents have observed better outcomes and lower drug-related toxicity[18-22]. However, amphotericin B remains a cornerstone of antifungal therapy for patients with opportunistic fungal infections. Recently, continuous infusion of amphotericin B has been found to reduce the incidence of nephrotoxicity and infusion-related reactions, compared with traditional administration of the same amount of the drug over 4–6 h[23-26] as well as the results from local randomized controlled study conducted at Ramathibodi Hospital [27]. This mode of administration of amphotericin B seems to be effective in reducing the adverse effects of amphotericin B [28] and is feasible in our setting. This prompted us to implement clinical practice policy based on continuous intravenous administration of amphotericin B deoxycholate in the patients hospitalized in the general medical wards at Siriraj Hospital.

Material and Method

A one-page evidence-based clinical practice policy on continuous intravenous administration of amphotericin B containing a description of the problem of using amphotericin B, recommendation on using continuous intravenous administration of amphotericin B, grade of recommendation and references was prepared. The clinical practice policy on continuous intravenous administration of amphotericin B was circulated to 10 general medical wards at Siriraj Hospital in March 2004. The decision to use continuous infusion or 4-to 6-hour infusion of amphotericin B was made by the responsible attending physicians. The use of medications to prevent infusion-related reactions was decided by attending physicians. The study was approved by the ethics committee on human research of the Faculty of Medicine, Siriraj Hospital. We collected the information on the patients who received amphotericin B who had serum creatinine <3 mg/dl. The patients who needed amphotericin B could receive a continuous infusion (CI group) or 4-to 6-hour infusion (RI group) of amphotericin B. In the patients who received continuous infusion of amphotericin B, amphotericin B at the appropriate dosage was added in 500 ml of 5% glucose without any additives and given intravenously as a continuous infusion over 24 hours. Medications to prevent any infusion-related reaction and intravenous saline were administered whenever appropriate.

Infusion-time was recorded in all cases. All infusion-related conditions were recorded including chills, nausea, vomiting, and phlebitis. Serum creatinine was measured at least twice a week and creatinine clearance (CrCl) was calculated by the Cockcroft-Gault formula[29]. Renal impairment was defined as a doubling of baseline serum creatinine and was calculated as a creatinine ratio (peak serum creatinine during amphotericin B administration/baseline serum creatinine).

The number of patients required for this study was assessed by the assumption that a rate of renal impairment in the CI group was 20% $\pm$ 7.5%. That was clinically less than 40% observed in hospitalized patients in the Department of Medicine who received 4-hour amphotericin B infusions in 2002, where 110 courses of CI would be needed at the two-sided significance level of 5%. Multivariate logistic regression analysis was used to adjust for potential confounding variables with regard to renal impairment and outcome. A Mann-Whitney U-test was used for median comparisons.

Results

Baseline characteristics

Of 166 courses of amphotericin B treatment in 148 patients, 102 courses (61.4%) in 91 patients were given by continuous intravenous administration of amphotericin B (CI group) and 64 courses (38.6%) in 57 patients were given by conventional 4-to 6-hour intravenous administration (RI group). The demographics of the patients in both groups are shown in Table 1. There were no significant differences in gender, duration of treatment or total dose of amphotericin B. However, the patients in the CI group were older than those in RI group (40 (15-74) vs 36 (16-68) years, p = 0.03) and had less HIV/AIDS than those in the RI group (21.6% vs 40.6%, p = 0.01). The number of patients in the CI group who received amphotericin B due to neutropenia with refractory fever was significantly greater than that in the RI group, 64.7 % vs 42.2% (p = 0.007) as shown in Table 2. Cryptococcal infections were more common in the patients in the RI group when compared with those in the CI group (34.4% vs 17.7%, p = 0.02). The baseline serum BUN was higher in the CI group than in the RI group (16.4 $\pm$ 14.5 mg/dl vs 13.9 $\pm$ 8.8, p = 0.03), but the baseline values of serum creatinine and calculated creatinine clearance were not significantly different between both groups. The use of medications to prevent infusion related reactions did not differ between the CI group and the RI group.

Outcomes

Nephrotoxicity, infusion-related reactions, and

Table 1. Demographic data of the patients

	Infusion rate		
	CI group (n = 91)	RI group (n = 57)	p-value
Median age, years (range)	40 (15-74)	36 (16-68)	0.03
Female, No. (%) of the patients	42 (41.2)	28 (43.8)	0.43
Median (range) days of treatment	11 (1-147)	14 (5-121)	0.11
Median (range) mg accumulative dose	400 (60-1880)	645 (180-5820)	0.17
Diagnosis, no.(%) of the patients			
- HIV/AIDS	22 (21.6)	26 (40.6)	0.01
- Acute myeloid leukemia	40 (39.2)	24 (37.5)	
- Non-Hodgkin's lymphoma	12 (11.8)	2 (3.1)	
- Acute lymphocytic leukemia	8 (7.8)	4 (6.3)	
- Severe aplastic anemia	6 (5.9)	1 (1.6)	
- Chronic myeloid leukemia	5 (4.9)	3 (4.7)	
- Others	9 (8.8)	4 (6.3)	
Concurrent treatment of nephrotoxic drugs	56 (54.9)	30 (46.9)	0.40
- Aminoglycosides	30 (29.4)	20 (31.3)	
- Vancomycin	14 (13.7)	4 (6.3)	
- Both	12 (11.8)	6 (9.4)	
- Others	1 (1)	0 (0)	

Table 2. Indications for amphotericin B treatment

	CI group (102 courses in 91 patients)	RI group (64 courses in 57 patients)	p-value
Refractory fever in neutropenia (ANC < 500/cumm) *	66 (64.7%)	27 (42.2%)	0.005
Cryptococcal infection	18 (17.7%)	22 (34.4%)	0.02
Aspergillus infection	8 (7.9%)	9 (14.1%)	
Penicillium infection	4 (3.9%)	0	
Histoplasma infection	2 (2%)	2 (3.1%)	
Mucormycoses	2 (2%)	1 (1.6%)	
Candidemia	2 (2%)	2 (3.1%)	
Cladophialophora bantiana brain abscess	0	1 (1.6%)	

* ANC means absolute neutrophil count

clinical outcomes of the patients are shown in Table 3. The nephrotoxicity was observed in 27.5% in the CI group and 39.1% in the RI group ($p = 0.2$), the relative risk of nephrotoxicity of the CI group when compared with that in the RI group was 0.70 (95% CI 0.45 to 1.09) and the relative risk reduction was 30% (95% CI -12% to 56%). The incidence of chills was 6.9% in the CI group and 26.6% in the RI group ($p = 0.001$), the relative risk was 0.26 (95% CI-0.11 to 0.59) and the relative risk reduction was 74.1%. There was no significant difference between nausea of 6.9% in the CI group and 12.5% in the RI group ($p = 0.169$) and phlebitis 22.5% in the CI group and 18.8% in the RI group ($p = 0.352$). Treatment failure was found in three patients with invasive aspergillosis who received continuous infusion of amphotericin B. Overall mortality at the end of therapy was significantly higher in the CI group (34.1%) than in the RI group (17.5%) ($p=0.05$), the relative risk was 1.35 (95% CI 1.06 to1.72). However most of the deaths in the CI group were unrelated to fungal infections. Chances of survival were significantly associated with age, febrile neutropenia, cryptococcal meningitis and AIDS from univariate analysis as shown in Table 4. However, a multivariate analysis

Table 3. Nephrotoxicity, infusion-related reactions and clinical outcomes of the patients

	CI group (102 courses in 91 patients)	RI group (64 courses in 57 patients)	p-value	Relative risk (95% CI)
Nephrotoxicity	28 (27.5%)	25 (39.1%)	0.16	0.70 (0.45-1.09)
Infusion related reactions				
- chills	7 (6.9%)	17 (26.6%)	0.001	0.26 (0.11-0.59)
- nausea	7 (6.9%)	8 (12.5%)	0.34	0.55 (0.21-1.44)
- phlebitis	23 (22.5)	2 (18.8)	0.352	1.20 (0.64-2.24)
Treatment failure	3 (2.9%)	0	0.3	not available
Overall mortality	31 (34.1%)	10 (17.5%)	0.05	1.35 (1.06-1.72)
Death due to fungal infections	2 (2.2%)	2 (3.5%)	0.6	0.6 (0.1-6.4)
Death due to other causes	29 (31.9%)	8 (14%)	0.02	2.8 (1.1-7.5)

Table 4. Univariate and multivariate analyses of overall mortality

	Outcome		Univariate analysis		Multivariate analysis	
	Survival	Death	p-value	OR (95%CI)	p-value	OR (95%CI)
Age > 36 year	54 (64.3%)	30 (35.7%)	0.021	0.78 (0.64-0.94)	0.057	
Febrile neutropenia	54 (65.1%)	29 (34.9%)	0.042	0.80 (0.66-0.97)	0.706	
AIDS	38 (88.4%)	5 (11.6%)	0.009	1.34 (1.13-1.60)	0.008	0.252 (0.091-0.696)
Cryptococcal meningitis	30 (90.9%)	3 (9.1%)	0.013	1.36 (1.15-1.61)	0.346	
Continuous infusion of amphotericin B	60 (65.9%)	31 (34.1%)	0.046	0.80 (0.66-0.97)	0.099	

revealed only AIDS was significantly associated with mortality, and continuous infusion of amphotericin B had not contributed to mortality.

Discussion

The clinical practice policy on continuous intravenous infusion of amphotericin B deoxycholate used in our study was based on the evidence from a randomized controlled study comparing continuous infusion of amphotericin B with 4-hour infusion regarding the incidence of the nephrotoxicity and infusion-related reactions [22]. The nephrotoxicity was decreased from 38% to 15% and infusion-related reactions from 63% to 20%. Subsequent studies also confirmed the safety and efficacy of continuous infusion of amphotericin B [23-26]. Therefore, our study was not intended to repeat any randomized controlled study, but rather to gain further knowledge. The implementation of the clinical practice policy in our study was only meant to raise awareness of the prescribers by disseminating such a clinical practice policy and the decision to use continuous infusion or 4-hour infusion of amphotericin B was made by the responsible attending physicians. As a result, only 61.4% of amphotericin B treatments followed the recommendation in the clinical practice policy. This observation confirmed the previous findings that dissemination of the guidelines was less effective than multifaceted interventions [30-31]. Since our study was not a randomized controlled trial, many important factors relevant to the severity of infection and prognosis of the treatment were not balanced between the group receiving continuous infusion of amphotericin B and that receiving 4-hour infusion. The patients in the CI group were older and had neutropenia with refractory fever significantly more often than those in the RI group. On the other hand, HIV/AIDS and cryptococcal meningitis were greater in the RI group. All these different factors seemed to be unfavorable for the patients in the continuous infusion group.

The incidence of nephrotoxicity in the RI group was 39%, comparable to 38% observed in the randomized controlled study. However, it was 27.5% in the CI group, higher than 15% observed in the randomized controlled study. As a result, the incidence of the nephrotoxicity of the patients in the CI group was not significantly different from that in the RI group. This could be explained by the small sample size since the relative risk reduction of nephrotoxicity was 30%.

We did not include fever as an infusion-related reaction because most of the patients who were receiving amphotericin B had fever at the beginning of amphotericin B infusion. Superficial thrombophlebitis from chemical irritation in the continuous infusion regimen was not significantly greater than that in the RI group.

Treatment failure was found in three patients in the CI group. All of them had invasive aspergillosis and two of them were switched to voriconazole therapy. These failures might not be related to continuous infusion of amphotericin B since it is well recognized that many patients of invasive aspergillosis do not respond well to amphotericin B deoxycholate. If these three patients had received 4-hour infusion of amphotericin B, they would not have responded to the treatment either. The overall mortality in the CI group was found to be significantly higher than that in the RI group. However, most of the deaths in the CI group were unrelated to fungal infections or continuous infusion of amphotericin B. The subgroup analyses of the mortality group revealed that the significant difference was confined to deaths from other causes. These observations might be due to the differences in many important factors of the patients between the CI group and the RI group mentioned earlier. Multivariate analysis also confirmed that continuous infusion of amphotericin B was not associated with an increase in mortality.

Conclusion

Continuous infusion of amphotericin B was associated with a decrease in infusion-related reactions and tended to have less nephrotoxicity than 4-to 6-hour infusion.

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การใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมงตามนโยบายเวชปฏิบัติ

ภาศรี มหารมณ์, วิษณุ ธรรมลิขิตกุล

วัตถุประสงค์: *เพื่อทราบผลการใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมงตามนโยบายเวชปฏิบัติในผู้ป่วยสามัญ ภาควิชาอายุรศาสตร์ โรงพยาบาลศิริราช เนื่องจากพบมีหลักฐานว่าการใช้ยาดังกล่าวลดพิษต่อไตได้*

วัสดุและวิธีการ: *เตรียมนโยบายเวชปฏิบัติเรื่องการใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่าง ต่อเนื่องใน 24 ชั่วโมงแทนการใช้ยา 4-6 ชั่วโมง และเผยแพร่นโยบายเวชปฏิบัตินี้แก่แพทย์ที่หอผู้ป่วยสามัญ ภาควิชาอายุรศาสตร์ ตั้งแต่เดือนมีนาคม พ.ศ. 2547 ถึงมีนาคม พ.ศ. 2549 นำข้อมูลมาวิเคราะห์ด้วยสถิติเชิงพรรณนา, การวิเคราะห์ univariate และ multivariate*

ผลการศึกษา: *มีการใช้ยาแอมโฟเทอริซินบีทั้งหมด 166 ครั้งในผู้ป่วย 148 ราย การใช้ยาในผู้ป่วย 102 ครั้ง (64%) เป็นการใช้ยาอย่างต่อเนื่อง 24 ชั่วโมง (CI) ส่วนอีก 64 ครั้ง (38.6%) ใช้ยา 4-6 ชั่วโมง (RI) อายุเฉลี่ยและภาวะไข้ในขณะที่มีเม็ดเลือดขาวต่ำในกลุ่ม CI มากกว่ากลุ่ม RI ส่วนกลุ่ม RI มีผู้ป่วยเอดส์ และเยื่อหุ้มสมองอักเสบจากเชื้อคริบโตคอคคัสมากกว่ากลุ่ม CI พบอัตราการเกิดพิษต่อไต 27.5 % ในกลุ่ม CI เทียบกับ 39.1% ในกลุ่ม RI (p = 0.164) ผลข้างเคียงโดยเฉพาะอาการสั่นขณะให้ยา 6.9% ในกลุ่ม CI เทียบกับ 26.6% ในกลุ่ม RI (p = 0.001) และพบอัตราตายรวมในกลุ่ม CI มากกว่ากลุ่ม RI อย่างมีนัยสำคัญ แต่เป็นอัตราตายจากสาเหตุอื่นที่ไม่ใช่จากการได้รับยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่อง*

สรุป: *การนำแนวทางเวชปฏิบัติใช้ยาแอมโฟเทอริซินบีหยดเข้าหลอดเลือดดำอย่างต่อเนื่องใน 24 ชั่วโมง มาใช้ในภาควิชาอายุรศาสตร์สามารถลดปฏิกิริยาของยาได้และมีแนวโน้มที่จะลดพิษต่อไตได้มากกว่าการใช้ยาหยดเข้าหลอดเลือดดำใน 4-6 ชั่วโมง*

Vancomycin Overuse in Siriraj Hospital

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Objective: *An emergence of vancomycin resistant organisms particularly vancomycin-resistant enterococci (VRE) has become a serious public health concern. To prevent and control the spread of vancomycin resistant organisms, the prudent use of vancomycin is strongly recommended by the Hospital Infection Control Practices Advisory Committee (HICPAC).*

Material and Method: *A 6-week prospective observational study of vancomycin use was conducted in hospitalized patients at Siriraj Hospital from February to March 2005. Indications of initiating and continuing vancomycin were categorized according to HICPAC recommendations. Factors related to the appropriateness of vancomycin use were also evaluated.*

Results: *At initiation, vancomycin was inappropriately and empirically prescribed 19/222 times (8.6%) and 166/222 times (74.8%), respectively. After microbiological results were obtained, the rate of inappropriate prescription continued 132/222 times (59.5%). Furthermore, inappropriate use was significantly correlated with the type of department. There was a higher rate in the Department of Pediatrics, Surgery and Ophthalmology when compared with that of the Department of Medicine ($p = 0.001$). The inappropriate use also correlated with topical use ($p < 0.001$), intravenous administration ($p = 0.012$) and no consultation with an infectious disease specialist ($p = 0.001$). The overuse did not improve the clinical outcome.*

Conclusion: *A substantial rate of inappropriate use of vancomycin was found in Siriraj Hospital. Intervention to improve appropriateness of vancomycin use should be urgently implemented to prevent and control the emergence of vancomycin resistant organisms.*

Keywords: *Anti-bacterial agents, Therapeutic use, HICPAC recommendation, Prospective observational studies, Vancomycin*

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Since 1989, a rapid increase in the incidence of infection and colonization with vancomycin-resistant enterococci (VRE) has been reported by US hospitals[1]. Currently, VRE has spread worldwide including Thailand. Hospitals in Thailand have reported the occurrence of VRE since 1995[2,3]. Furthermore, VRE have become a major global health concern. The problem has been addressed from the aspect of the clinical outcomes and in respect of the economic burden of health care facilities. VRE cause a widespread pragmatic problem on treatment because most VRE are also resistant to antibiotics recommended for treatment, such as a combination of ampicillin and aminoglycoside. The number of effective antibiotics against VRE infections is limited. An emergence of vancomycin resistance in clinical isolates of *Staphylococcus aureus* or *Staphylococcus epidermidis* is also a serious public

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health concern. In 1992, Noble and colleagues showed that the vanA gene could be transferred by cell to cell mating between enterococci and staphylococci[4]. Recently, Weigel and colleagues reported an in-vivo transfer of vancomycin resistant gene (vanA) from *Enterococcus fecalis* to a methicillin-resistant *S. aureus* (MRSA) capable of producing *S. aureus* resistant to vancomycin (VRSA)[5]. However, clinical isolates of staphylococci containing the vanB, vanC, or vanD genes have not been reported. This process may simultaneously originate heterogeneous Vancomycin intermediate resistant *S. aureus* (Hetero-VISA)[6,7] and Vancomycin Resistant *S. epidermidis* (VRSE)[8].

An increased use of vancomycin has led to selective pressure, and the subsequent appearance of VRE, Hetero-VISA, and VISA followed by VRSA has alarmed physicians and microbiologists[9]. Previous studies have shown that a sustained increase of vancomycin overuse in recent years was associated with the emergence of VRE and other resistant gram positive organisms[10,11], and a substantial reduction inpatient vancomycin use was associated with declining VRE isolation rates[12].

The Hospital Infection Control Practices Advisory Committee (HICPAC) recommended the following elements for prevention and control of the spread of vancomycin resistance, with a special focus on VRE[13].

a) Prudent vancomycin use by clinicians as shown in the appendix attached,

b) Education of hospital staff regarding the problem of vancomycin resistance,

c) Early detection and prompt reporting of vancomycin resistance in enterococci and other gram-positive microorganisms by the hospital microbiology laboratory,

d) Immediate implementation of appropriate infection-control measures to prevent person-to-person transmission of VRE.

According to the HICPAC recommendations, the inappropriateness of vancomycin use in tertiary care hospitals ranged from 17-83%[12,14-18]. In Thailand, the information on overuse of vancomycin is limited. Therefore, we conducted this study to explore the magnitude and associated factors of vancomycin overuse in Siriraj Hospital, a 2000-bed university hospital.

Material and Method

Subjects and Study Design

The study was approved by The Ethics Committee on Human Research of the Faculty of Medicine Siriraj Hospital. This prospective observational study was conducted at Siriraj Hospital, a 2,000-bed academic tertiary-care hospital in Bangkok, from February 1st to March 14th, 2005. All new vancomycin prescriptions for hospitalized patients were collected. The patients who received at least one dose of vancomycin were enrolled into the study. Demographics, clinical information, and microbiological study results were recorded. Indications for initiating and continuing vancomycin use after receiving microbiological information were evaluated. Factors that may have related to the appropriateness of vancomycin prescription, which included department patient care, suspected site of infection, route of vancomycin use, and infectious disease (ID) consultation, were also evaluated.

Outcome Measurement

The appropriateness of vancomycin use at initiation and continuation was determined by using explicit criteria developed by the HICPAC[13] as summarized in the appendix. Dosing, route and duration of vancomycin administration were also evaluated. Infectious disease (ID) specialist consultation was classified as i) absence of ID specialist consultation, ii) presence and implementation of ID specialist suggestion and iii) presence but non-implementation of ID specialist suggestion. Clinical outcome was finally evaluated at the end of vancomycin use and divided into 6 categories as shown in Table 1

Statistical analysis

Data were expressed as percentage and mean $\pm$ SD for nominal and continuous variables, respectively. Analyses were performed using SPSS 11.5 (SPSS Inc, Chicago, Illinois). Nominal variables were compared by a Chi-square test or Fisher's exact test and continuous variables were compared by a two-tailed unpaired t-test or Mann-Whitney U test as appropriate. The statistically significant factors were confirmed by multivariate analysis using a logistic regression model. A p value < 0.05 was considered significant.

Results

Patient characteristics

Two hundred and twenty two courses of vancomycin on 221 patients were included. One patient was treated twice. Patients' characteristics, site of infection and administration route are summarized in Table 2. The total amount of vancomycin used was 1,713 grams, averaging 7.72 grams per course. The cost of the vancomycin was 1,161,414 baht, based on the

Table 1. Therapeutic outcome

Definition of therapeutic outcomes
1. Cure: a complete resolution of symptoms and signs of infection
2. Partial response: an incomplete resolution of symptoms and signs of infection
3. No response: no resolution and progression of symptoms and signs of infection
4. Infectious death: a death with suspected infectious cause
5. Non-infectious death: a death with no suspected infectious cause
6. Indeterminate outcome: no evaluation possible

Table 2. Demographic data of 222 courses of prescription for 221 patients

	Number	Percentage (%)
Patient characteristics (N = 222)		
Gender (Male : Female)	119:103	
Mean Age (yr)	46.65	
Department (N = 222)		
Medicine	99	44.6
Surgery	39	17.6
Ophthalmology	39	17.6
Pediatrics	36	16.2
Orthopedics	5	2.3
Obstetrics and Gynecology	4	1.8
Site of suspected infection* (N = 222)		
Primary bacteremia	45	20.3
Catheter associated infection	33	14.9
Major organs infection	87	39.2
Eye-ENT infection	42	18.9
Antibiotic associated colitis (AAC)	7	3.2
No Evidence of infection	8	3.6
Administration route* (may be more than 1 route)		
Intravenous injection (IV)	181	81.5
Oral administration (PO)	8	3.6
Topical administration (Tp)	27	12.2
Ophthalmic injection (Op)	12	5.4
Intra-cavitary injection (IC)	2	0.9
Antibiotic Lock Therapy (ALT)	2	0.9

* see appendix

Table 3. Appropriateness of vancomycin use

	Number	Percentage (%)
At initiation of treatment		
Appropriate	37	16.7
Inappropriate	19	8.6
Empirical	166	74.8
For continuation of treatment		
Appropriate	90	40.5
Inappropriate	132	59.5

current price of Edicin® 339 baht/ 500 mg.

Vancomycin-use data

The distribution of the appropriateness of vancomycin used is presented in Table 3. According to the HICPAC recommendation, 19 (8.6%), 37 (16.7%) and 166 episodes (74.8%) of vancomycin use were appropriate, inappropriate and empirical respectively at initiation of vancomycin. At continuation, we found that 132 of 222 episodes (59.5%) were inappropriately continued.

Associated factors for inappropriateness of use of vancomycin

We did not find any correlation between the proportion of inappropriateness at the initiation phase and all of our influencing factors. On the contrary, inappropriateness of vancomycin use was significantly associated with the department that cared for the patient, ID-consultation pattern, site of infection and administration route of vancomycin during the continuation phase as shown in Table 4. Our data showed that inappropriate use of vancomycin was significantly lower in the Department of Medicine compared to other departments. Furthermore, the group that followed the ID suggestion was lower compared to either the non-implementation group or absence of ID suggestion group. On the other hand, we found that treating EYE-ENT infection was the most common site of vancomycin overuse. Moreover, inappropriateness of vancomycin use was significantly higher in topical and intravenous routes and it was significantly lower in oral routes.

Table 4. Inappropriateness of vancomycin use at continuation according to services, ID consultation pattern, site of infection and route of vancomycin use

Factors	Total	Inappropriateness of vancomycin use		p-value
		Number	Percentage (%)	
Total number	222	132	59.5	
Services				
Medicine	99	40	40.4	0.001[a]
Surgery	39	28	71.8	
Pediatrics	36	25	69.4	
Ophthalmology	39	37	94.9	
ID-consultation				
Implementation of suggestion	35	10	28.6	0.001[b]
Non-implementation	14	12	85.7	
No consultation	174	110	63.6	
Suspected site of infection				
Primary bacteremia	45	31	68.9	0.001[c]
Catheter associated infection	33	13	39.4	
Major organs infection	87	42	48.3	
Eye-ENT infection	42	39	92.9	
AAC	7	0	0.0	
No evidence of infection	8	7	87.5	
Route(s) of vancomycin use				
IV		100	55.2	0.012[d]
Tp		26	96.3	<0.001[e]
PO		0	0.0	0.002[f]

Note: The rates of inappropriate use of vancomycin were significantly lower in (a) the Medicine Department compared to other departments, (b) in the ID implementation group compared to others by pair wise comparisons using the Bonferroni correction. The rate of inappropriate use of vancomycin was significantly higher (c) in the treating EYE-ENT infection group compared to the other sites by pair wise comparisons using the Bonferroni correction. The rates of inappropriate use of vancomycin were significantly higher in (d) the intravenous route and (e) the topical route and it was significantly lower in (f) the oral route by using Fisher's exact test

Table 5. Therapeutic outcome

Therapeutic outcome	Appropriateness of vancomycin use		p-value
	Appropriate (%)	Inappropriate (%)	
Total number	90 (40.5)	132 (59.5)	
Cure or partial response	66 (73.3)	80 (60.6)	0.031*
No response or infectious death	21 (23.3)	35 (26.5)	
Non-infectious death orindeterminate outcome	3 (3.3)	17 (12.9)	

*The rate of cure and partial response was significantly higher in the appropriate use group compared to the inappropriate use group by pair wise comparisons using the Bonferroni correction

Therapeutic outcome

Appropriate use of vancomycin resulted in a significantly higher percentage in the cure and partial response rate (73.3%) than in the inappropriate use group (60.6%; p = 0.031) as shown in Table 5. This observation indicated that an overuse of vancomycin did not significantly improve the clinical outcome.

Discussion

From our study, a very high rate of inappropriate use of vancomycin (59.5%) was observed particularly in the Department of Ophthalmology compared with previous reports that found inappropriate use in the Intensive care unit[19], Transplant Unit[19] and the Department of Pediatrics[20].The inappropriateness of vancomycin use was significantly higher in non-medical wards. The most common reasons for inappropriate use of vancomycin were (1) treating infected corneal ulcers with topical vancomycin eye drops, (2) treating infections caused by beta-lactam susceptible organisms (3) treating contaminated organisms in blood culture taken from asymptomatic patients.

Regarding the increasing incidence of bacterial keratitis caused by MRSA and Methicillin resistant *S. epidermidis* (MRSE)[21,22], the recommendation of the Endophthalmitis Vitrectomy Study suggested using topical vancomycin eye drops to treat postoperative endophthalmitis[23]. Therefore, vancomycin has become one of the most extensively used topical antibiotics in ophthalmology[24]. The Department of Ophthalmology in our hospital has adopted a practice policy for treating severe corneal ulcer with vancomycin eye drop. This policy is inconsistent with the HICPAC recommendation that discourage the use of topical vancomycin for reasons stared. In our study, topical vancomycin eye drops were used in 38 patients having infected corneal ulcers. Of these, one patient was documented as having infection caused by beta-lactam resistant organisms.

Moreover, we found that most vancomycin uses were not discontinued even though the microbiological test results revealed beta-lactam sensitive organisms. This might be a misconception of physicians that vancomycin is a superior antibiotic to beta-lactam for treatment of staphylococcal infections.

The burden of inappropriateness of vancomycin use in this study alarms us and an effective strategy is urgently needed to correct it. Vancomycin restriction policy seems to be risky in a hospital where MRSA is prevalent, such as our hospital (41.5% of *S. aureus* isolates were methicillin resistant)[25]. However, most of MRSA bacteremia or infection is gradually progressed. The delayed vancomycin treatment did not compromise patients' survival rates[26,27] and was safe even in the worst-case scenario such as clinically significant MRSA bacteremia[18,28].

Conclusion

Sixty percent of vancomycin prescriptions for hospitalized patients in Siriraj Hospital demonstrated inappropriate overuse. This practice not only worsened the clinical outcome, but also consumed unnecessary expenditure of 5 million baht per year. Moreover, the potential emergence of vancomycin resistant gram positive organisms may have been increased. This should be considered as one of the major problems of antibiotic use and an effective strategy to reduce this problem must be considered.

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Appendix

Recommendations for prudent vancomycin use[13]
(Adapted from the HICPAC recommendations)

1. Situations in which the use of vancomycin is considered appropriate:

- Treatment of infections caused by beta-lactam resistant gram-positive microorganisms.
- Treatment of infections caused by gram-positive microorganisms in patients who have serious allergies to beta-lactam antimicrobials.
- When antibiotic-associated colitis fails to respond to metronidazole therapy or is severe and potentially life-threatening.
- Endocarditis prophylaxis in high risk patients following certain procedures (following the American Heart Association recommendation)
- Prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices at institutions that have a high rate of infections caused by beta-lactam resistant gram positive microorganisms.

2. Situations in which the use of vancomycin is considered inappropriate:

- Routine surgical prophylaxis other than in a non life-threatening beta-lactam allergic patient.
- Empiric antimicrobial therapy for a febrile neutropenic patient, unless there is initial evidence of an infection caused by gram-positive microorganisms at institutions that have a high rate of beta-lactam resistance.
- Treatment in response to a single blood culture positive for coagulase-negative staphylococcus, if other blood cultures taken during the same time frame are negative.
- Continued empiric use for presumed infections in patients whose cultures are negative for beta-lactam-resistant gram-positive microorganisms.
- Systemic or local (e.g., antibiotic lock) prophylaxis for infection or colonization of indwelling central or peripheral intravascular catheters.
- Selective decontamination of the digestive tract.
- Eradication of MRSA colonization.
- Primary treatment of antibiotic-associated colitis.
- Routine prophylaxis for very low-birth weight infant, patients on continuous ambulatory peritoneal dialysis or hemodialysis.
- Treatment (chosen for dosing convenience) of infections caused by beta-lactam-sensitive gram-positive microorganisms in patients who have renal failure.
- Use of vancomycin solution for topical application or irrigation.

Definition and terms

Suspected sites of infection

1. Primary bacteremia was defined as the positive blood culture (at least one specimen) of likely uncontaminated organisms with clinical signs of systemic infection where the focal site of infection couldn't be identified.

2. Catheter-associated infection was defined as the clinical evidence of insertion site or tunnel infection with or without positive blood culture.

3. Major organ(s) infection was defined as the infection of major organs; lung, heart, urinary tract, brain, peritoneal cavity, soft tissue, musculoskeletal system.

4. EYE-ENT infection was defined as the infection of the eye-ear-nose-throat system

5. Antibiotic associated colitis (AAC) was defined as the diarrhea that appeared after antibiotic administration and was confirmed by colonoscopic gross finding or *C. difficile* was isolated.

6. No evidence of infection was defined as those patients who have no clinical sign of systemic inflammatory response syndrome (SIRS) nor clinical signs and symptoms of focal site of infection. (Perioperative antibiotic prophylaxis was included in this category.)

Route(s) of vancomycin use were classified as

1. Intravenous injection (IV)

2. Oral administration (PO)

3. Topical form (Tp); ophthalmic and otic solution administration (topical solution was prepared by dissolving 500 mg of commercial vancomycin powder for injection with 10 ml. of balanced salt solution)

4. Ophthalmic injection (Op); subconjunctival, intra-vitreous and intra-aqueous injection

5. Intra-cavitary injection(IC); intra-peritoneal, intra-articular, intra-ventricular and intra-thecal injection, etc.

6. Antibiotic Lock therapy (ALT); the method involves instilling a highly concentrated antibiotic solution into a catheter lumen and allowing the solution to dwell for a specified time period for the purpose of sterilizing the lumen[29].

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การใช้ยาแวนโคมัยซินเกินความจำเป็นในโรงพยาบาลศิริราช

ภิญโญ รัตนาอัมพวัลย์, วิษณุ ธรรมลิขิตกุล, กุลกัญญา โชคไพบูลย์กิจ, ดรินทร์ โล่ห์ศิริวัฒน์, นลินี อัศวโภคี

วัตถุประสงค์: *เพื่อทราบการใช้ยาแวนโคมัยซินอย่างไม่เหมาะสมในโรงพยาบาลศิริราช*
วัสดุและวิธีการ: *ศึกษาการใช้ยาแวนโคมัยซินแก่ผู้ป่วยในทุกรายในโรงพยาบาลศิริราชในช่วงเดือนกุมภาพันธ์ ถึงมีนาคม พ.ศ.2548 เป็นระยะเวลา 6 สัปดาห์ โดยเก็บข้อมูลการเริ่มใช้ยาตามข้อบ่งชี้ และการใช้ยาต่อเนื่อง ภายหลังทราบผลการเพาะเชื้อและความไวต่อยาปฏิชีวนะ เมื่อเปรียบเทียบกับคำแนะนำการใช้ยาของคณะกรรมการควบคุมการติดเชื้อของCDC (Centers for Disease Control) รวมถึงศึกษาปัจจัยอื่น ๆ ซึ่งอาจมีผลกระทบ*
ผลการศึกษา: *ช่วงเริ่มต้นมีการสั่งยาแวนโคมัยซินอย่างไม่เหมาะสม 19 ราย (ร้อยละ 8.6) และสั่งยาไปก่อนระหว่างรอผลการตรวจหาเชื้อ 166 ราย (ร้อยละ 74.8) หลังจากทราบผลการตรวจหาเชื้อทั้งหมดแล้ว แพทย์ยังคงใช้ยาต่ออย่างไม่เหมาะสม 132 ราย (ร้อยละ 59.5) กลุ่มผู้ป่วยที่มีอัตราการใช้ยาอย่างไม่เหมาะสมต่ำกว่ากลุ่มอื่น ๆ ได้แก่ ผู้ป่วยภาควิชาอายุรศาสตร์ ($p < 0.001$) และการใช้ยาตามคำแนะนำของสาขาวิชาโรคติดเชื้อ ($p = 0.001$) ส่วนรูปแบบการบริหารยาที่มักมีการใช้อย่างไม่เหมาะสมคือ ยาในรูปหยอดตา ($p < 0.001$) หรือฉีดเข้าหลอดเลือดดำ ($p = 0.012$) นอกจากนี้ผู้ป่วยกลุ่มที่มีการใช้ยาเกินความจำเป็นไม่ได้ทำให้ผลการรักษาดีขึ้น*
สรุป: *โรงพยาบาลศิริราชมีการใช้ยาแวนโคมัยซินอย่างไม่เหมาะสมสูง ดังนั้นจึงควรหาแนวทางแก้ไขอย่างเร่งด่วนเพื่อป้องกันการเพิ่มขึ้นของเชื้อดื้อยาในอนาคต*

Utilization of Calculated Low Density Lipoprotein Cholesterol and Measured Low Density Lipoprotein Cholesterol in Siriraj Hospital

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A study to determine the utilization of calculated low density lipoprotein (c-LDL) cholesterol and measured low density lipoprotein (m-LDL) cholesterol was conducted. The test results of total cholesterol, triglyceride, HDL-cholesterol and m-LDL-cholesterol from the same individuals aged ≥ 18 years who had the tests done at the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital during January to December 2004 were retrieved. The c-LDL-cholesterol level was computed using Friedewald formula. There were two data sets i.e. the m-LDL-cholesterol cut-off level derivation data set (784 subjects) and the m-LDL-cholesterol cut-off level validation data set (800 subjects). The study results revealed: 1) 2.6% of the subjects had blood triglyceride > 400 mg/dl hence c-LDL-cholesterol could not be computed, 2) the correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels from both data sets was very good (r > 0.95, p < 0.001), 3) the m-LDL-cholesterol levels were usually higher than c-LDL-cholesterol levels, 4) the m-LDL-cholesterol cut-off level derivation data set showed that m-LDL-cholesterol < 87, > 143, > 188, > 233 and > 254 mg/dl were highly correlated with c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl respectively, 5) an application of m-LDL-cholesterol cut-off levels derived from the m-LDL-cholesterol cut-off level derivation data set to the m-LDL-cholesterol cut-off level validation data set showed that m-LDL-cholesterol < 87, > 143, > 188, > 233 and > 254 mg/dl had accuracy in predicting c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl of 100%, 99.7%, 100%, 100% and 100% respectively, 6) the use of m-LDL-cholesterol levels as a guide for initiating lipid-lowering agents based on cut-off values of c-LDL-cholesterol levels led to an overuse of lipid-lowering agents in 3.6% to 42.9% of the patients and 7) Nomogram for transforming m-LDL-cholesterol to c-LDL-cholesterol was developed as well as a formula for transforming m-LDL-cholesterol to c-LDL-cholesterol (c-LDL-cholesterol = 0.89 ◊ m-LDL-cholesterol). Therefore, m-LDL-cholesterol assay has a very limited use in managing individuals with suspected or known dyslipidemia. The use of m-LDL-cholesterol level as a guide for management of abnormal LDL-cholesterol conditions leads to an overuse of lipid lowering medications and an enormous expense of m-LDL-cholesterol assay.

Keywords: *Low density lipoprotein cholesterol, LDL*

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Low density lipoprotein (LDL) is a lipoprotein consisting of cholesterol (40%-50%), phospholipids (20%-25%) and triglyceride (5%-15%). Elevation of blood LDL-cholesterol is recognized as one of the major risk factors for atherosclerosis and ischemic heart disease and a lowering of blood LDL-cholesterol could diminish the risk of ischemic heart disease[1-3]. The third report of the national cholesterol education program (NCEP III) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) classifies blood LDL-cholesterol levels as normal (blood LDL-cholesterol < 100 mg/dl), nearly-normal (blood LDL-cholesterol 100-129 mg/dl), nearly-high (blood LDL-cholesterol 130-159 mg/dl), high (blood LDL-cholesterol 160-189 mg/dl) and very high (blood LDL-cholesterol >190 mg/dl)[4]. Management of individuals with elevated blood LDL-cholesterol includes diet control, exercise, and drugs. It is suggested that 1) individuals with ≤ 1 cardiovascular risk factor who have a chance of developing ischemic heart disease of less than 10% within 10 years should receive treatment if their blood LDL-cholesterol is ≥ 190 mg/dl 2) individuals with ≥ 2 cardiovascular risk factor who have a chance of developing ischemic heart disease of less than 10% within 10 years should receive treatment if their blood LDL-cholesterol is ≥ 160 mg/dl 3) people with ≥ 2 cardiovascular risk factors who have a chance of developing ischemic heart disease of 10% to 20% within 10 years, or patients with diabetes mellitus or ischemic heart disease who have a chance of developing ischemic heart disease of more than 20% within 10 years should receive treatment if their blood LDL-cholesterol is ≥ 130 mg/dl and they should have behavior modification if their blood LDL-cholesterol is ≥ 100 mg./dl. The aforementioned blood LDL-cholesterol thresholds are based on LDL-cholesterol calculated from total cholesterol, triglyceride and high density lipoprotein (HDL) cholesterol using Friedewald's formula[5]. Calculated LDL-cholesterol (c-LDL) is equivalent to total cholesterol – HDL-cholesterol – triglyceride/5. A direct measurement for blood LDL-cholesterol (m-LDL) has been available over the past decade and this assay has become popular. The cost of an m-LDL-cholesterol assay in Siriraj Hospital is 150 baht, whereas c-LDL-cholesterol is provided without any additional cost if total cholesterol, triglyceride and HDL-cholesterol are ordered.

The objectives of the study were to determine the pattern of utilization of m-LDL-cholesterol and to determine cut-off thresholds of m-LDL-cholesterol that predict c-LDL-cholesterol cut-off levels for initiating appropriate management as recommended in NCEP III.

Material and Method

The test results of total cholesterol, triglyceride, HDL-cholesterol and m-LDL-cholesterol from the same individuals aged ≥ 18 years during January to December 2004 were retrieved from the database of the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital. Calculated LDL-cholesterol was computed using Freidewald formula. There were two data sets. The first data set was the m-LDL-cholesterol cut-off level derivation data set. It was the test results of 784 individuals randomly selected from those who had the tests during January to June 2004. The medical records of these individuals were analyzed for demographics, cardiovascular risk factors and managements they received. The second data set was the m-LDL-cholesterol cut-off level validation data set. It was the test results of 800 individuals randomly selected from those who had the tests during July to December 2004. The data were analyzed by descriptive statistics and inferential statistics where appropriate. The correlation between c-LDL-cholesterol and m-LDL-cholesterol levels was determined by Pearson's Product Moment Correlation Coefficient. The formula for transforming m-LDL-cholesterol level to c-LDL-cholesterol level was generated from linear regression analysis. A p-value ≤ 0.05 was considered statistically significant.

Results

1. Analyses of the test results of the m-LDL-cholesterol cut-off level derivation data set (784 individuals) revealed the following:

Twenty individuals (2.6%) had blood triglyceride > 400 mg/dl hence c-LDL-cholesterol could not be computed.

Seven hundred and sixty four individuals with blood triglyceride < 400 mg/dl had demographics and clinical features as shown in Table 1. 63.4% of them were females. A mean age was 59.4 years, mean body weight was 61.5 Kg, mean height was 159.4 cm, and mean body mass index (BMI) was 24.75 Kg/m^2 22.3% of them had ischemic heart diseases, 1.6% had ≤ 1 cardiovascular risk factor, 23.6% had ≥ 2 cardiovascular risk factors; and the status of cardiovascular risk factors was not available in 52.6%.

The lipid profiles of 764 individuals with blood triglyceride < 400 mg./dl. are shown in Table 2. The m-LDL-cholesterol levels were higher than c-LDL-cholesterol levels.

Table 1. Demographics and cardiovascular risk factors of 764 individuals who had blood triglyceride < 400 mg/dl

Characteristic	
Females	484 (63.4%)
Mean age (SD)	59.4 yr (13.07 yr)
Median age (Range)	60.3 yr (18-89 yr)
Mean body weight (SD)	59.4 Kg (13.07 Kg)
Median body weight (Range)	60.0 Kg (33-102 Kg)
Mean height (SD)	159.4 cm (8.09 cm)
Median height (Range)	158.0 cm (140-181 cm)
Mean BMI (SD)	24.75 Kg/m^2 (3.94 Kg/m^2)
Median BMI (Range)	24.51 Kg/m^2 (17.19-37.25 Kg/m^2)
Cardiovascular Risk Factors Ischemic Heart Disease	170 (22.3%)
≥ 2 factors	180 (23.6%)
0-1 factor	12 (1.6%)
not available	402 (52.6%)

Table 2. Lipid profiles of 764 individuals who had blood triglyceride < 400 mg/dl

	Range	Mean (SD)	Median
Cholesterol (mg/dl)	72-383	204.6 (46.77)	201.0
HDL-cholesterol (mg/dl)	9-122	53.2 (16.51)	51.6
Triglyceride (mg/dl)	18-398	131.9 (67.79)	115.0
m-LDL-cholesterol (mg/dl)	33-295	145.6 (44.98)	142.0
c-LDL-cholesterol (mg/dl)	9-267	124.9 (41.08)	122.3

The distribution of the difference between m-LDL-cholesterol and c-LDL-cholesterol levels from 764 individuals with blood triglyceride < 400 mg/dl is shown in Table 3. 91% of them had a difference ≤ 25%.

The correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels is shown in Fig. 1. The correlation was statistically significant ($p < 0.001$) and the magnitude of the correlation was very high.

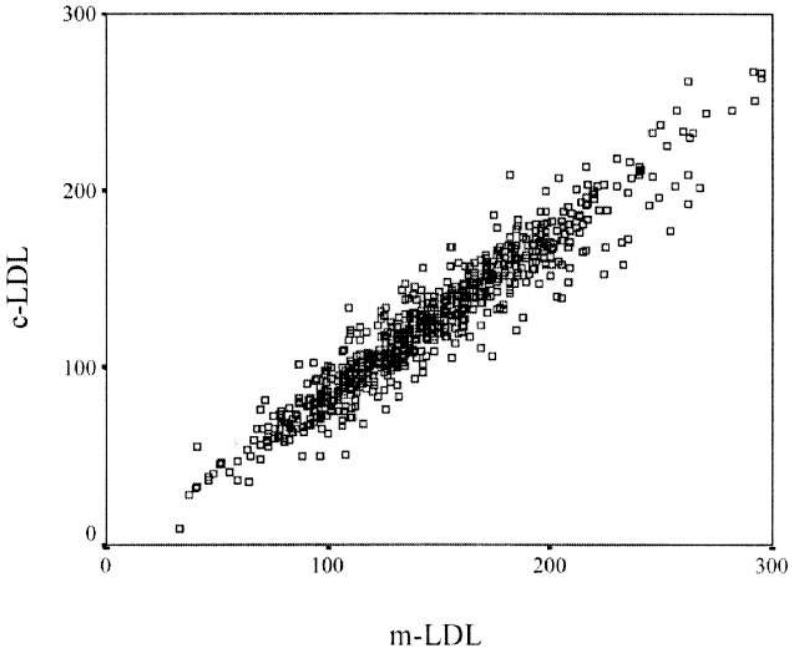
The predictive levels of m-LDL-cholesterol to determine c-LDL-cholesterol levels of < 100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl were < 87, > 143, > 188, > 233 and > 254 mg/dl respectively (Table 4).

2. Analyses of the test results of the m-LDL-cholesterol cut-off level validation data set (800 individuals) revealed the following:

The individuals with blood triglyceride < 400 mg/dl had a mean age of 57.9 years and 61.8% of them were females. There was no statistically significant difference in demographics between the individuals in

Table 3. The distribution of the differences between m-LDL-cholesterol levels and c-LDL-cholesterol levels from 764 individuals with blood triglyceride < 400 mg/dl

Difference between c-LDL- cholesterol and m-LDL- cholesterol	N (%)
± 5%	53 (6.9)
± 10%	139 (18.2)
± 15%	221 (28.9)
± 20%	183 (24.0)
± 25%	98 (12.8)
± 30%	36 (12.8)
± 35%	21 (2.7)
± 40%	7 (0.9)
± 45%	3 (0.4)
± 50%	1 (0.1)
± 55%	1 (0.1)
± 60%	1 (0.1)



Pearson Correlation Coefficient (r) = 0.956, $p < 0.001$

Fig. 1 The correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels from 764 individuals with blood triglyceride < 400 mg/dl

Table 4. The predictive values of m-LDL-cholesterol level to determine c-LDL-cholesterol level

m-LDL-cholesterol (mg/dl)	c-LDL-cholesterol (mg/dl)
<87	<100
>143	≥100
>188	≥130
>233	≥160
>254	≥190

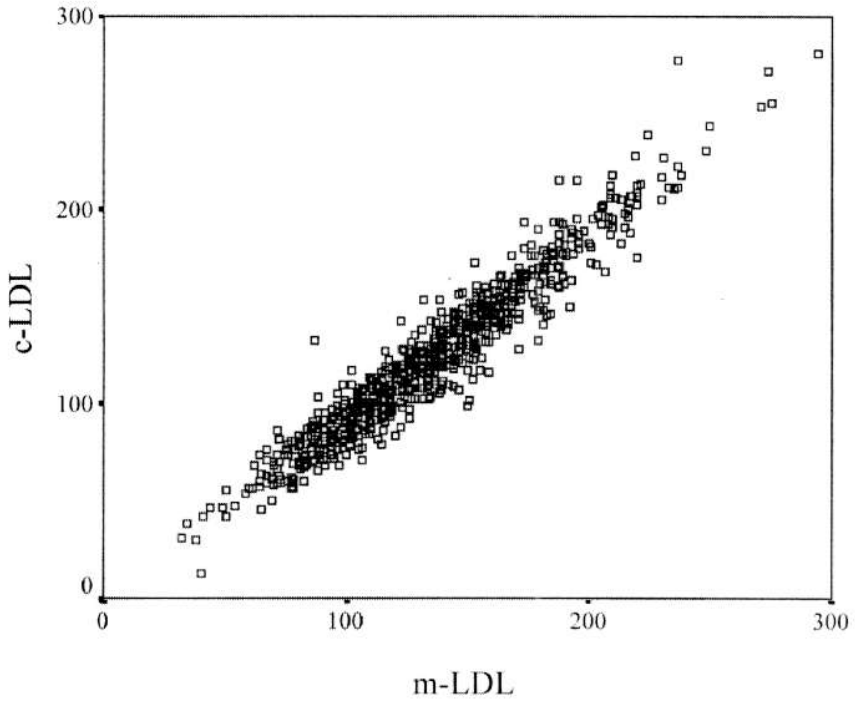
the m-LDL-cholesterol cut-off value derivation data set and the m-LDL-cholesterol cut-off value validation data set.

The lipid profiles of 800 individuals with blood triglyceride < 400 mg/dl are shown in Table 5. The m-LDL-cholesterol values were higher than c-LDL cholesterol values similar to those observed in 764 individuals in the m-LDL-cholesterol cut-off value derivation data set.

The correlation between c-LDL-cholesterol and m-LDL-cholesterol levels is shown in Fig. 2. The correlation was statistically significant ($p < 0.001$) and the magnitude of the correlation was very high.

Table 5. Lipid profiles of 800 individuals who had blood triglyceride < 400 mg/dl

	Range	Mean (SD)	Median
Cholesterol (mg/dl)	45-366	201.8 (45.78)	200
HDL-cholesterol (mg/dl)	6-116	51.5 (14.31)	50
Triglyceride (mg/dl)	32-398	131.8 (66.68)	117
m-LDL-cholesterol (mg/dl)	32-294	134.9 (40.66)	133
c-LDL-cholesterol (mg/dl)	13-281	124 (40.21)	120



Pearson Correlation Coefficient (r) = 0.963, p < 0.001

Fig. 2 The correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels from 800 individuals with blood triglyceride < 400 mg/dl

An application of m-LDL-cholesterol cut-off values derived from the m-LDL-cholesterol cut-off value derivation data set to the m-LDL-cholesterol cut-off value validation data set showed that m-LDL-cholesterol < 87, > 143, > 188, > 233 and > 254 mg/dl had accuracy in predicting c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl of 100%, 99.7%, 100%, 100% and 100% respectively.

3. The nomogram to be used for transforming m-LDL-cholesterol level to c-LDL-cholesterol level was made from the test results of 1,564 individuals who had blood triglyceride < 400 mg/dl and is shown in Fig. 3.

4. A formula for transforming m-LDL-cholesterol level to c-LDL-cholesterol level was generated from the test results of 1,564 individuals who had blood triglyceride < 400 mg./dl. using a linear regression analysis. The c-LDL-cholesterol was approximately 0.89 x m-LDL-cholesterol.

5. Analyses of a sample of individuals whose baseline m-LDL-cholesterol levels were available and who had received lipid lowering drugs based on m-LDL-cholesterol levels revealed the following observations:

Out of 28 individuals with baseline m-LDL-cholesterol level > 100 mg/dl, 27 had c-LDL-cholesterol level ≥ 100 mg/dl. Hence the treatment was inappropriately given in 1/28 (3.6%) of cases.

Out of 26 individuals with baseline m-LDL-cholesterol level > 130 mg/dl, 25 had c-LDL-cholesterol level ≥ 130 mg/dl. Hence the treatment was inappropriately given in 1/26 (3.8%) of cases.

Out of 20 individuals with baseline m-LDL-cholesterol level > 160 mg/dl, 16 had c-LDL-cholesterol level ≥ 160 mg/dl. Hence the treatment was inappropriately given in 4/20 (20%) of cases.

Out of seven individuals with baseline m-LDL-cholesterol level >190 mg./dl, four had c-LDL-cholesterol level ≥ 190 mg/dl. Hence the treatment was inappropriately given in 3/7 (42.9%) of cases.

Discussion

Our study confirmed the findings from other reports that c-LDL-cholesterol levels are strongly

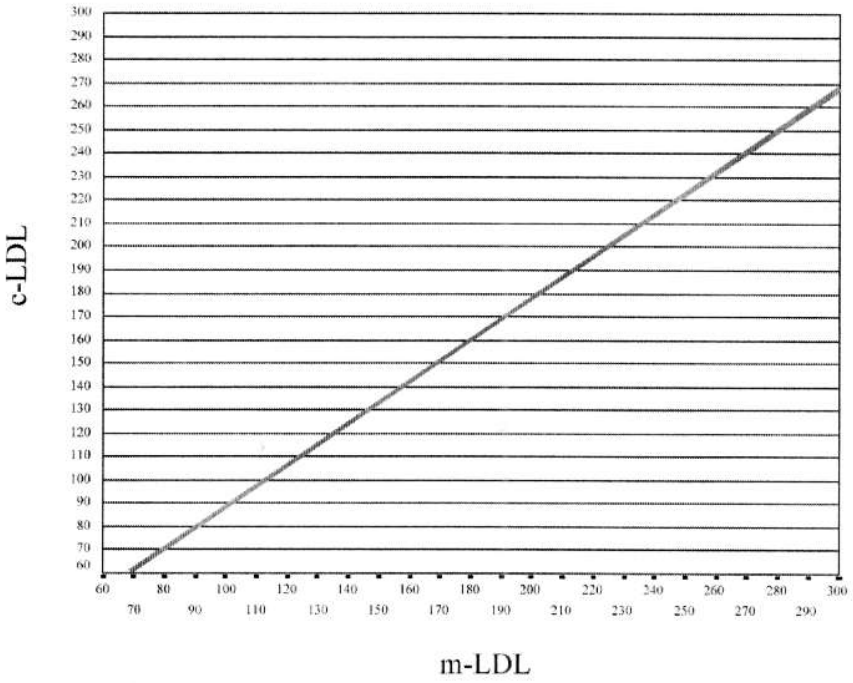


Fig. 3 Nomogram for transforming m-LDL-cholesterol level to c-LDL-cholesterol level

correlated with m-LDL-cholesterol levels[6-9]. However, the correlation between c-LDL-cholesterol levels and m-LDL-cholesterol levels is not perfect. As a result, the values of m-LDL-cholesterol levels are not exactly the same as c-LDL-cholesterol levels and m-LDL-cholesterol levels are usually higher than c-LDL-cholesterol levels. The LDL-cholesterol cut-off values for initiating appropriate management recommended in NCEPIII are based on c-LDL-cholesterol levels. Therefore, m-LDL-cholesterol levels could not replace c-LDL-cholesterol levels if one wants to use the LDL-cholesterol cut-off values recommended in NCEPIII as a guide for management of patients with dyslipidemia. Our study demonstrated that 3.6% to 42.9% of the patients with an elevated LDL-cholesterol level received unnecessary lipid-lowering agents if the LDL-cholesterol cut-off values recommended in NCEIII were used for m-LDL-cholesterol levels. The m-LDL-cholesterol cut-off values of <87, >143, >188, >233 and >254 mg/dl were found to be accurate to predict the c-LDL-cholesterol levels of <100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl respectively. Moreover, we observed that only 2.6% of the individuals who received lipid profile testing had blood triglyceride >400 mg/dl and c-LDL-cholesterol could not be computed. Hence the m-LDL-cholesterol assay is needed for this group and the cut-off thresholds for initiating lipid-lowering agents should be >143, >188, >233 and >254 mg/dl instead of <100, ≥ 100, ≥ 130, ≥ 160 and ≥ 190 mg/dl respectively. Until more solid evidence on the clinical benefit to patients receiving management according to the cut-off values of m-LDL-cholesterol is available, the cut-off values of c-LDL-cholesterol should not be applied to m-LDL-cholesterol test results to guide the treatment on patients. If the m-LDL-cholesterol assay becomes necessary such as in those with blood triglyceride >400 mg/dl, the cut-off values of >143, >188, >233 and >254 mg/dl should be considered or the m-LDL-cholesterol level should be transformed to c-LDL-cholesterol level using the nomogram in figure 3 or the m-LDL-cholesterol level should be transformed to the c-LDL-cholesterol level using the formula of c-LDL-cholesterol ~ 0.89 x m-LDL-cholesterol prior to initiating appropriate management. The aforementioned nomogram or formula for transforming m-LDL-cholesterol level to c-LDL-cholesterol level is also useful for health care providers who use m-LDL-cholesterol for monitoring the response to treatment, since the cost of a

m-LDL-cholesterol assay (150 baht) is less than the cost of a combination of total cholesterol, HDL-cholesterol and triglyceride (170 baht). In conclusion, m-LDL-cholesterol assay has a very limited use in managing individuals with suspected or known dyslipidemia. The use of m-LDL-cholesterol level as a guide for the management of abnormal LDL-cholesterol conditions leads to an overuse of lipid lowering medications and an enormous expense in m-LDL-cholesterol assay costs.

Acknowledgement

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การใช้การตรวจ low density lipoprotein cholesterol ที่ได้จากการคำนวณและ low density lipoprotein cholesterol ที่ได้จากการวัดโดยตรงในโรงพยาบาลศิริราช

วนิดา วงศ์ถิรพร, ลักษมี วัฒนมงคลศิลป์, สุทธิ์จรี เกียรติวิชญ์, นิตยา มิ่งวิวัฒน์, สุนี ธนกำธร, นิศารัตน์ โอภาสเกียรติกุล, วิษณุ ธรรมลิขิตกุล

คณะผู้วิจัยได้ศึกษาการใช้การตรวจ low density lipoprotein (c-LDL) cholesterol ที่ได้จากการคำนวณและ low density lipoprotein (m-LDL) cholesterol ที่ได้จากการวัดโดยตรง ในโรงพยาบาลศิริราชโดยนำผลการตรวจระดับของ total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol และ m-LDL-cholesterol จากคนเดียวกันที่อายุ 18 ปีหรือมากกว่าและได้รับการตรวจระดับไขมันในเลือดที่ภาควิชาพยาธิวิทยาคลินิกระหว่างเดือนมกราคมถึงธันวาคม พ.ศ. 2547 ส่วนหนึ่งมาคำนวณค่า c-LDL-cholesterol ด้วยสูตรของ Friedewald แล้วนำผลดังกล่าวมาวิเคราะห์ความสัมพันธ์กับระดับ m-LDL-cholesterol ข้อมูลที่นำมาศึกษามี 2 ชุด ได้แก่ ข้อมูลชุดแรกที่นำมาวิเคราะห์หาเกณฑ์ของค่า m-LDL-cholesterol (derivation data set) จำนวน 784 คนและข้อมูลชุดที่สองที่นำมาทดสอบความแม่นยำของเกณฑ์ของค่า m-LDL-cholesterol ที่ได้จากข้อมูลชุดแรก (validation data set) จำนวน 800 คน พบว่า 1) ผู้มารับการตรวจร้อยละ 2.6 มีค่า triglyceride มากกว่า 400 มก./ดล. ซึ่งไม่สามารถคำนวณค่า c-LDL-cholesterol ได้ 2) ค่า c-LDL-cholesterol และ m-LDL-cholesterol ของข้อมูลทั้ง 2 ชุดมีความสัมพันธ์กันอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) และความสัมพันธ์มีขนาดมากกว่า 0.95, 3) ระดับของ m-LDL-cholesterol มักสูงกว่า c-LDL cholesterol 4) ค่า m-LDL-cholesterol cut-off < 87, > 143, > 188, > 233 and > 254 มก./ดล. จะสัมพันธ์กับค่า c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 และ ≥ 190 มก./ดล. ตามลำดับ 5) เมื่อนำเกณฑ์ดังกล่าวจากข้อมูลชุดแรกไปประยุกต์ใช้กับข้อมูลชุดที่สองพบว่าค่า m-LDL-cholesterol < 87, > 143, > 188, > 233 and > 254 มก./ดล. มีความแม่นยำในการทำนายค่า c-LDL-cholesterol < 100, ≥ 100, ≥ 130, ≥ 160 และ ≥ 190 มก./ดล. ร้อยละ 100, 99.7, 100, 100 และ 100 ตามลำดับ 6) เมื่อวิเคราะห์ผู้ป่วยที่มีค่า m-LDL-cholesterol ก่อนการรักษาและได้รับการรักษาด้วยยาลดไขมันในเลือดโดยอาศัยระดับของ m-LDL-cholesterol เป็นแนวทางในการรักษาพบว่าผู้ป่วยร้อยละ 3.6 ถึง 42.9 ได้รับยาลดไขมันโดยไม่จำเป็น 7) ได้สร้าง nomogram สำหรับแปลงค่า m-LDL-cholesterol ให้เป็น c-LDL-cholesterol และสูตรการแปลง m-LDL-cholesterol ให้เป็น c-LDL-cholesterol โดย c-LDL-cholesterol จะมีค่า 0.89 x m-LDL-cholesterol ผลการศึกษานี้แสดงว่า m-LDL-cholesterol มีที่ใช้น้อยมาก การใช้การตรวจ m-LDL-cholesterol โดยอาศัยเกณฑ์ระดับ c-LDL-cholesterol เป็นแนวทางในการรักษาผู้ป่วยทำให้ผู้ป่วยส่วนหนึ่งได้รับยาลดไขมันในเลือดโดยไม่จำเป็นและยังสิ้นเปลืองค่าใช้จ่ายในการตรวจ m-LDL-cholesterol ด้วย

Epidemiology of *Acinetobacter baumannii* Infections in Siriraj Hospital 2002

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ABSTRACT

Objective: To determine the epidemiology of *A.baumannii* infections in Siriraj Hospital in 2002.

Methods: From January to December 2002, we prospectively studied hospitalized patients in Siriraj Hospital who had *A.baumannii* isolated from their clinical specimens.

Results: During the study period, *A.baumannii* was isolated from clinical specimens of 208 cases. Eighty-six patients (41.3%) had *A.baumannii* infections whereas 122 patients (58.7%) had *A.baumannii* colonization. Of the 86 patients with *A.baumannii* infections, 54.7% were males and 45.3% were females. The mean age of patients was 56.1 years. Ninety-eight percent of the infections were hospital-acquired. The patients developed infection after an average of 26 days of hospitalization. Fifty-two percent of the patients were in the general wards, whereas 48% of them were in ICU. The common sites of infection were respiratory tract and skin and soft tissues. Factors associated with *A.baumannii* infection were identified in 98.8% of the patients. The most common factors were prior use of antibiotics especially ceftazidime and indwelling medical devices. The susceptibility of *A.baumannii* to carbapenems, aminoglycosides, beta-lactam/ beta-lactamase inhibitors, co-trimoxazole, fluoroquinolone, 4th generation cephalosporins and 3rd generation cephalosporins was 32%, 16%, 12 %, 9%, 7%, 4% and 3%, respectively. Fifty-seven percent of *A.baumannii* isolates were resistant to all antimicrobials currently available in Thailand. The overall mortality rate of the patients infected with *A.baumannii* was 54.7%.

Conclusion: Most *A.baumannii* infections in Siriraj were hospital-acquired. The most common site of infection was the respiratory tract. The majority of *A.baumannii* isolates was multi-drug resistant. The mortality rate of *A.baumannii* infections was high.

Keywords: *Acinetobacter baumannii* infections; Epidemiology

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Acinetobacter spp. is aerobic gram negative bacilli. Healthy individuals can harbor this organism on their skin especially over the moist areas. Skin colonization rate of in hospitalized patients was significantly more than that in healthy individuals.[1,2] This observation implies that the patients should acquire the organism while hospitalization. *Acinetobacter* spp. is also commonly found in hospital environments and it can be transmitted to the patients via hospital personnel and contaminated instruments or devices.[1,2] *Acinetobacter baumannii* is the most common species of Acinetobacter causing infections in human. Over the past decade, there have been many reports on *Acinetobacter* spp. as a common causative pathogen in intensive care unit patients and the infection was associated with indwelling medical devices, e.g., ventilator-associated pneumonia, catheter-associated urinary tract infection, blood stream infection associated with intravascular devices.[1,2] *Acinetobacter* spp. is usually resistant to many antibiotics including cephalosporins, aminoglycosides and fluoroquinolones due to various resistance mechanisms.[3] *Acinetobacter* spp. is one of the most common causes of hospital acquired infections in Thailand.[4] To our knowledge there has been no report on epidemiology of *Acinetobacter baumannii* infections in Thailand. Therefore, this study attempted to determine the clinical features, risk factors, clinical course and outcomes of patients infected with *A.baumannii* in Siriraj Hospital in 2002.

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MATERIALS AND METHODS

This is a prospective study conducted in Siriraj Hospital, a tertiary care university hospital, from January to December 2002. The hospitalized patients who had *A. baumannii* isolated from their clinical specimens submit-

TABLE 1. Underlying diseases of 86 patients with *A.baumannii* infections.

Diseases	N (%)*
Cerebrovascular disease	27 (31.4)
Hypertension	24 (27.9)
Diabetes mellitus	23 (26.7)
Cancer	14 (16.3)
Chronic renal failure	14 (16.3)
Ischemic heart disease	10 (11.6)
Chronic obstructive pulmonary disease	9 (10.5)
Neutropenia	4 (4.7)
Cirrhosis	1 (1.2)
Others	23 (26.7)

* The patient could have more than one disease.

ted to Microbiology Laboratory were notified to the investigators. Then clinical information and microbiological information of the patients were collected, and the patients were followed until they left the hospital or died. The collected information was analyzed by descriptive statistics.

RESULTS

A. baumannii was isolated from clinical specimens of 208 patients during the study period. Eighty-six patients (41.3%) were infected, i.e. the patients who had clinical features of infection at the site where *A. baumannii* was isolated, whereas 122 (58.7%) were colonization, i.e., the patients who did not have clinical features of infection at the site where *A. baumannii* was isolated or the patients who had clinical features of infection at the site where the organism was isolated but the infection was caused by other organisms. Patients with *A. baumannii* infections were males in 54.7% and the mean age was 56.1 years with a range from 6 days to 91 years. Ninety percent of *A. baumannii* infected patients had underlying diseases as shown in Table 1. The common underlying diseases were cerebrovascular diseases, hypertension and diabetes mellitus. Forty-eight percent of the patients were hospitalized in general wards whereas 52% were in intensive care units. The patients were admitted to medical, surgical and pediatrics department in 61%, 23% and 9%, respectively. Almost all infections (97.7%) were hospital-acquired: which were those occurred in patients after hospitalization for longer than 48 hours. Almost all patients (98.8%) had factors that might be associated with A. baumannii infections as shown in Table 2. The most common factors

TABLE 2. The factors associated with *A.baumannii* infections in 86 patients.

Factors	N (%)*
Antibiotics	85 (98.8)
Peripheral intravascular devices	82 (95.3)
Urinary catheter	73 (84.9)
Nasogastric tube	69 (80.2)
Endotracheal tube	62 (72.1)
Ventilator	62 (72.1)
Surgery	39 (45.3)
Central intravascular devices	38 (44.2)
Immunosuppressives	9 (10.5)
Chemotherapy	5 (5.8)
Parenteral nutritution	5 (5.8)
Others	27 (31.4)

* The patient could have more than one factor.

TABLE 3. The sites of *A.baumannii* infections in 86 patients.

Sites of infection	N (%)*
Respiratory tract	59 (68.6)
Skin and soft tissues	17 (19.8)
Bacteremia	6 (7.0)
Urinary tract	4 (4.7)
Nervous system	3 (3.5)
Gastrointestinal tract	3 (3.5)
Others	1 (1.2)

* The patient could have more than one site of infection.

were prior use of antibiotics especially ceftazidime and indwelling medical devices. The patients developed infections after an average of 26 days of hospitalization. The sites of A. baumannii infections are shown in Table 3. The common sites were respiratory tract and skin and soft tissues. Seventy-one percent of the patients had *A. baumannii* as a single pathogen, whereas 29% had mixed infections with others such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Patients with respiratory tract infections tended to have mixed infections more often than infections in other sites. Almost all patients (98.8%) received various antibiotics prior to having *A. baumannii* infections as shown in Table 4. Ceftazidime was an antibiotic commonly given to the patients. The susceptibility of *A. baumannii* to carbapenems, aminoglycosides, beta-lactam/ beta-lactamase inhibitors, co-trimoxazole, fluoroquinolone, 4th generation cephalosporins and 3rd generation cephalosporins was 32%, 16%, 12 %, 9%, 7%, 4% and 3%, respectively. *A. baumannii* was resistant to all antimicrobials currently available in Thailand in 57% of the isolates. The patients with *A. baumannii* infections were usually treated with meropenem, imipenem and cefoperazone/sulbactam as shown in Table 5. The overall mortality rate of patients infected with *A. baumannii* was 54.7% and most of them died of multi-drug resistant *A. baumannii* infections. The mortality rate in those patients infected with pan-drug resistant *A. baumannii* was higher than those infected with sensitive strains.

DISCUSSION

Our study found that less than 50% of the patients whose *A. baumannii* was present in their clinical speci-

TABLE 4. Antibiotics given to the patients prior to developing *A.baumannii* infections in 86 patients.

Antibiotics	N (%)*
Ceftazidime	28 (32.6)
Meropenem	21 (24.4)
Ceftriaxone	18 (20.9)
Amikacin	14 (16.3)
Vancomycin	14 (16.3)
Imipenem	11 (12.8)
Metronidazole	11 (12.8)
Cefoperazone/sulbactam	10 (11.6)
Ciprofloxacin	9 (10.5)
Cefotaxime	7 (8.1)
Netilmicin	7 (8.1)
Clindamycin	6 (7.0)
Cefepime	5 (5.8)
Amphotericin B	5 (5.8)
Fluconazole	1 (1.2)
Others	23 (26.7)

* The patient could have more than one antibiotic.

TABLE 5. Antibiotics for treating *A.baumannii* infections in 86 patients.

Antibiotics	N (%)*
Meropenem	23 (26.7)
Imipenem	14 (16.3)
Cefoperazone/sulbactam	9 (10.5)
Amikacin	8 (9.3)
Netilmicin	5 (5.8)
Ciprofloxacin	4 (4.7)
Ceftazidime	3 (3.5)
Others	29 (33.7)

* The patient could have more than one antibiotic.

mens were infections, whereas the majority were colonization. Therefore, healthcare providers should be aware of this observation and should avoid antibiotic treatment of patients with *A. baumannii* colonization. *Acinetobacter* spp. has been recognized as an important nosocomial pathogen over the past decade. It is usually resistant to many antibiotics empirically used for infections caused by other aerobic gram negative bacilli such as cephalosporins. As a result, the mortality of patient infected with *Acinetobacter* spp. is rather high. A report in Thailand revealed that *Acinetobacter* spp. was the most common cause of ventilatory associated pneumonia in a university hospital.[5] Our study observed that *A. baumannii* infections are more common in middle-age males. However, the patients could be babies and the elderly as seen in other studies.[6-10] This study also confirmed the observations made by others that almost all patients infected with *A. baumannii* were hospitalized longer than 48 hours. The other two patients who developed *A. baumannii* infections within 48 hours of hospitalization were those who were transferred to Siriraj Hospital from other hospitals. However, our study revealed that *A. baumannii* infections were similarly distributed in general wards and intensive care units (ICU) that was different from other studies.[11] This discrepancy could be explained by the fact that many patients in general wards in Siriraj Hospital were seriously ill but they were unable to be transferred to ICU due to a limited number of ICU beds. The average duration of hospitalization until developing *A. baumannii* infections in our study was 26 days that was longer than 10 to 14 days found in other studies.[8,12,14] However, is has been found that a long duration of hospitalization was associated with *A. baumannii* infections.[6,14] Although *A. baumannii* can cause infections in any organs, the common sites of infections seen in our study were respiratory tract and skin and soft tissues similar to other studies.[14,15] Factors found to be associated with *A. baumannii* infections were, namely: cancer, indwelling medical devices, antibiotics, parenteral nutrition, surgery, severe underlying diseases and duration of hospitalization.[12-15] Our study also observed that antibiotics, especially ceftazidime, and indwelling medical devices were common in patients infected with *A. baumannii*. In vitro susceptibility of *A. baumannii* revealed that the pathogen was usually resistant to antibiotics active for other aerobic gram negative bacilli and more than 50% of the isolates were resistant to all antibiotics currently available in Thailand. Therefore, antibiotics to be used for treating *A. baumannii* infections were limited. These included carbapenems, aminoglycosides and beta-lactam/ beta-lactamase inhibitors. An overall mortality of patients with *A. baumannii* infections was 54.7% and most of them died of multi-drug resistant *A. baumannii* infections. Polymyxins were found to be safe and effective for treatment of multi-drug resistant *A. baumannii* infections.[16] *In vitro* studies of polymyxins against *A.baumannii* resistant to all antibiotics currently available in Thailand revealed that all isolates were susceptible to polymyxins.[17] Polymyxin E has just been available in Thailand since January 2005 and the clinical trial on safety and efficacy of polymyxin E for treatment of A.baumannii infections is being conducted in Siriraj Hospital. New antibiotics such as glycylcycline were found to be active against multi-drug resistant *A.baumannii* and these antibiotics should have a role in treatment of *A.baumannii* infections in the near future.

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บทคัดย่อ

ระบาดวิทยาของการติดเชื้อ *Acinetobacter baumannii* ในโรงพยาบาลศิริราช พ.ศ. 2545

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วัตถุประสงค์: เพื่อทราบระบาดวิทยาการติดเชื้อ *A.baumannii* ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชในปี พ.ศ. 2545

วิธีการ: เฝ้าระวังการตรวจพบเชื้อ *A.baumannii* ที่ห้องปฏิบัติการจุลชีววิทยาจากตัวอย่างตรวจที่เก็บจากผู้ป่วยที่รับไว้รักษาโรงพยาบาลศิริราชตั้งแต่วันที่ 1 มกราคม ถึง 31 ธันวาคม 2545 แล้วติดตามผู้ป่วยที่มีการติดเชื้อดังกล่าวโดยเก็บข้อมูลต่าง ๆ ที่เกี่ยวข้องเพื่อนำมาวิเคราะห์

ผลการศึกษา: มีผู้ป่วยที่แยกได้เชื้อ *A.baumannii* จากสิ่งส่งตรวจจำนวน 208 ราย ในจำนวนนี้เป็นการติดเชื้อจำนวน 86 ราย (ร้อยละ 41.3) ส่วนอีก 122 ราย (ร้อยละ 58.7) เป็น colonization, ผู้ป่วยที่ติดเชื้อ 86 รายเป็นชายร้อยละ 54.7 และหญิงร้อยละ 45.3, ผู้ป่วยมีอายุเฉลี่ย 56.1 ปี, การติดเชื้อร้อยละ 98 เป็นการติดเชื้อในโรงพยาบาล, ระยะเวลาเฉลี่ยของการอยู่ในโรงพยาบาลก่อนมีการติดเชื้อ 26 วัน, ผู้ป่วยร้อยละ 52 อยู่ที่หอผู้ป่วยสามัญและผู้ป่วยร้อยละ 48 อยู่ที่หออภิบาล, ตำแหน่งที่มีการติดเชื้อบ่อยคือระบบการหายใจและบาดแผล, ผู้ป่วยร้อยละ 98.8 มีปัจจัยที่สัมพันธ์กับการติดเชื้อโดยปัจจัยที่พบบ่อยคือการได้รับยาต้านจุลชีพโดยเฉพาะอย่างยิ่ง ceftazidime และการมีสายเข้าสู่ร่างกาย, อัตราการดื้อยาของเชื้อ *A.baumannii* ต่อ carbapenems, aminoglycosides, beta-lactam/beta-lactamase inhibitors, co-trimoxazole, fluoroquinolone, 4th generation cephalosporins และ 3rd generation cephalosporins เป็นร้อยละ 32, 16, 12, 9, 7, 4 และ 3 ตามลำดับ เชื้อ *A.baumannii* ร้อยละ 57 ดื้อต่อยาต้านจุลชีพทุกขนานที่มีในประเทศไทย และผู้ป่วยที่ติดเชื้อ *A.baumannii* เสียชีวิตร้อยละ 54.7

สรุป: การติดเชื้อ *A.baumannii* ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราชเกือบทั้งหมดเป็นการติดเชื้อในโรงพยาบาล การติดเชื้อส่วนมากเป็นที่ระบบการหายใจ เชื้อก่อโรคส่วนมากดื้อต่อยาต้านจุลชีพทุกขนานที่มีในประเทศไทย และผู้ป่วยที่ติดเชื้อนี้มีอัตราตายสูง

Stenotrophomonas maltophilia Infections in Hospitalized Patients at Siriraj Hospital

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ABSTRACT

Ninety-seven strains of *Stenotrophomonas maltophilia* isolated from 62 patients hospitalized at Siriraj Hospital from September 2005 to February 2006 were studied. Ninety-two strains (94.8%) were isolated from respiratory secretions and five strains (5.2%) were from blood. Only 39.3% of the patients who had *S. maltophilia* isolated from their clinical specimens had infections. All *S. maltophilia* infections were hospital acquired and the infected patients had underlying diseases, multiple medical devices and received multiple antibiotics prior to *S. maltophilia* infections. Pneumonia was the most common site of infections. *S. maltophilia* was susceptible to co-trimoxazole in 68.8% of the isolates. The overall mortality of the patients with *S. maltophilia* infections was 45.5%.

Keywords: Hospitalized patients; infections; *Stenotrophomonas maltophilia*

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Stenotrophomonas maltophilia is a non-fermentative aerobic gram-negative bacillus formerly classified as *Pseudomonas.*[1] *S. maltophilia* is usually found in a variety of aquatic environments. *S. maltophilia* is a frequent colonizer of fluids used in the hospital setting i.e. irrigation solutions and intravenous fluids, and of patient secretions e.g., respiratory secretions, urine, wound exudates. *S. maltophilia* is an organism of low virulence and is an infrequent pathogen in humans. *S. maltophilia* must bypass normal host defenses to cause human infection. For example, if an intravenous infusion fluid contains a large amount of *S. maltophilia*, then direct injection into the bloodstream may result in blood stream infection. *S. maltophilia* has been recognized as an increasingly important nosocomial pathogen causing pneumonia, bacteremia and other infections especially in debilitated and immunocompromised cancer or hematologic malignancy patients.[1-4] Infection with *S. maltophilia* is difficult to treat since effective antibiotics against *S. maltophilia* are limited and co-trimoxazole is an antibiotic of choice.[1-5]

The objective of the study was to describe the demographics, clinical features and outcomes of hospitalized patients at Siriraj Hospital who had *S. maltophilia* isolated from their clinical specimens.

MATERIALS AND METHODS

S. maltophilia isolated from the clinical specimens collected from the patients hospitalized at Siriraj Hospital during a six-month period from September 2005 to February 2006 were included. The medical records of the patients with a presence of *S. maltophilia* in their clinical specimens were reviewed.

RESULTS

There were 97 isolates of *S. maltophilia* from 62 patients hospitalized at Siriraj Hospital during the study period. Ninety-two strains (94.8%) were isolated from respiratory secretions and five strains (5.2%) were from blood. Forty patients (64.5%) were males and 22 (35.5%) were females. The mean age of the patients was 53.1 years (median age 62 years) with an age ranged from 1 month to 90 years. Thirty patients (48.4%) were hospitalized at intensive care units (ICU). The medical records of 56 patients were available for review. Twenty-nine patients (51.8%) were medical patients and 19 (33.9%) and 6 (10.7%) were surgical and pediatrics patients respectively. Forty-nine patients (87.5%) had underlying severe or chronic diseases such as cancer, diabetes mellitus, hypertension, cerebrovascular diseases, ischemic heart diseases. *S. maltophilia* isolated from the respiratory secretions of 34 patients (60.7%) were considered colonization since the patients did not have clinical features of *S. maltophilia* pneumonia. Of 22 patients with *S. maltophilia* infections, 17 patients (77.3%) had pneumonia, 4 patients (18.2%) had bacteremia and 1 patient (4.5%) had pneumonia and bacteremia. All episodes of *S. maltophilia* infections were hospital-acquired. All patients with *S. maltophilia* infections had underlying diseases, multiple medical devices including central venous catheter, endotracheal tubes, urethral catheters, nasogastric tubes, and had received multiple antibiotics prior to developing *S. maltophilia* infections. Eighteen patients (81.8%) were hospitalized in the ICU. In vitro susceptibility of co-

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trimoxazole against 77 isolates of *S. maltophilia* revealed that 53 isolates (68.8%) were susceptible. Fifteen patients with *S. maltophilia* infections received co-trimoxazole and 10 patients survived whereas 7 patients received other antibiotics and only 2 patients survived. The overall mortality of the patients with *S. maltophilia* infections was 45.5%.

DISCUSSION

We found that most isolates of *S. maltophilia* from respiratory secretions were colonizations, all patients with *S. maltophilia* infections had underlying diseases, multiple medical devices and had received multiple antibiotics prior to developing the infections; and a high mortality of patients with *S. maltophilia* infections confirmed the observations made earlier by others.[1-6] The responsible healthcare personnel should be aware that most of the *S. maltophilia* strains isolated from respiratory secretions were not infections and these patients did not need antibiotics specific for *S. maltophilia*. The recovery of *S. maltophilia* from respiratory secretions should be regarded as colonization until proven otherwise and a potential pathogenic role should be evaluated by an infectious disease consultant. Although *S. maltophilia* usually is resistant to aminoglycosides, antipseudomonal penicillins, and antipseudomonal third-generation cephalosporins, it usually is susceptible to co-trimoxazole. *S. maltophilia* isolated from hospitalized patients at Siriraj Hospital was less susceptible to co-trimoxazole than that in other studies.[5, 7-10] Therefore new antibiotics are needed for therapy of *S. maltophilia* infections. Tigecycline was found to be active against most isolates of *S. maltophilia*[11, 12] and this antibiotic might be beneficial for therapy of *S. maltophilia* infections. Polymyxin B was found to be active against *S. maltophilia*[13] whereas colistin (polymyxin E) was inactive against *S. maltophilia* in another study.[10] In vitro synergy of colistin with rifampin and trimethoprim/sulfamethoxazole on multidrug-resistant *S. maltophilia* was observed[14] and antibiotic combination could be another measure for therapy of *S. maltophilia* infections. Since all *S. maltophilia* infections in our study were hospital-acquired, the choice of antibiotic therapy was limited and the mortality rate was high. Effective infection control measures should be employed in order to prevent *S. maltophilia* colonizations and infections in hospitalized patients. Sources of *S. maltophilia* colonization include personnel (hands, antiseptic soaps, hand lotion), respiratory equipment and/or fluids (ultrasonic nebulizers, inhalation medications, respirator tubing condensate), IV lines and/or fluids (IV solutions, central venous catheters, pressure monitoring devices - pressure transducer fluids), urine and/or fluids (indwelling urinary catheters, urometers, irrigation solutions). Effective measures for decontamination of *S. maltophilia* in these sources and a control of patient-to-patient spread of the organism should be attempted and is of concern.

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บทคัดย่อ

การติดเชื้อ *Stenotrophomonas maltophilia* ในผู้ป่วยที่รับไว้รักษาในโรงพยาบาลศิริราช

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คณะผู้วิจัยได้ศึกษาเชื้อ *Stenotrophomonas maltophilia* จำนวน 97 สายพันธุ์จากเสมหะและเลือดที่แยกได้จากผู้ป่วย 62 คนที่รับไว้รักษาในโรงพยาบาลศิริราช ระหว่างเดือนกันยายน พ.ศ. 2548 ถึงเดือนกุมภาพันธ์ พ.ศ. 2549 พบว่าเชื้อร้อยละ 94.8 แยกได้จากเสมหะ และร้อยละ 5.2 แยกได้จากเลือด ผู้ป่วยเพียงร้อยละ 39.3 เท่านั้นที่มีการติดเชื้อ *S. maltophilia* การติดเชื้อทั้งหมดเกิดในผู้ป่วยที่รับไว้รักษาโรงพยาบาลที่มีโรคประจำตัว ได้รับสายหรือท่อสอดใส่เข้าสู่ร่างกาย และได้รับยาต้านจุลชีพหลายขนานก่อนมีการติดเชื้อดังกล่าว การติดเชื้อส่วนมากคือปอดอักเสบ เชื้อ *S. maltophilia* ร้อยละ 68.8 ไวต่อยา co-trimoxazole ผู้ป่วยติดเชื้อ *S. maltophilia* มีอัตราตายร้อยละ 45.5

Clinical Study of *Morus Alba* Linn. on Glycemic Control and Blood Lipids in Patients with Type 2 Diabetes: A Preliminary Study

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ABSTRACT

Effects of *Morus alba*-leaf extracts on glycemic control and blood lipids were carried out in 27 patients with newly diagnosed type 2 diabetes. Water extracts of *Morus alba* leaves at a dosage of 700 mg were given to the patients thrice daily for 8 weeks. The patients did not receive any concomitant medications for diabetes or hyperlipidemia. The mean fasting plasma glucose levels at baseline, week 2, week 4, week 6 and week 8 were 155.1, 179, 173.6, 183.9 and 185.8 mg/dl, respectively (p=0.04). The mean glycosylated hemoglobin levels at baseline and week 8 were 7.6% and 8.4%, respectively (p=0.002). The mean blood total cholesterol levels at baseline, week 2, week 4, week 6 and week 8 were 229.6, 211.2, 210.2, 204.5 and 199.4 mg/dl, respectively (p<0.001). The mean blood triglyceride levels at baseline, week 2, week 4, week 6 and week 8 were 235.4, 191.3, 174.5, 183.5 and 168.2 mg/dl, respectively (p=0.001). No patients experienced side effects of the treatment. Laboratory results on CBC, urine, blood electrolytes, renal function and liver function at baseline, week 2, week 4, week 6 and week 8 were not significantly different. *Morus alba*-leaf extracts have no hypoglycemic effect but they may exert lipid lowering effects.

Keywords: Hyperglycemia; hyperlipidemia; *Morus alba*; type 2 diabetes

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The risk of cardiovascular diseases is increased in patients with poorly controlled diabetes mellitus and hyperlipidemia.[1,2] A number of medicinal herbs were reported to yield hypoglycemic effect.[3-5] *Morus alba* was found to contain hypoglycemic and lipid lowering effects in animals.[6-9] A toxicity study of *Morus alba* leaves revealed no remarkable acute and sub-chronic toxicities.[10] Water infusion of *Morus alba* leaves has been widely used in Thailand over the past decades. The claims for promoting consumption of *Morus alba* leaves infusion are its beneficial effects on glycemic control and hyperlipidemia in patients with diabetes.

The objective of this study was to determine whether *Morus alba*-leaf extracts improved blood glucose, glycosylated hemoglobin, total cholesterol and triglyceride levels in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Department for Development of Thai Traditional and Alternative Medicine, Ministry of Public Health, Thailand. The study site was Pathumthani Hospital, Pathumthani, Thailand. The study was conducted from October 2004 to May 2005.

Patients

The eligible patients were newly diagnosed type 2 diabetes mellitus (fasting plasma glucose between 127 to 200 mg/dl) aged 40 to 70 years. The patient was excluded if he/she had acute complications of diabetes or received anti-diabetics or lipid lowering agents or was allergic to *Morus alba*.

Plant extractions, preparations and administration

Mulberry leaves (*Morus alba*, Nakornratchasima 50) were obtained from the Department of Agriculture, Ministry of Agriculture and Co-Operatives in Plant Genetics Conservation Project. The sample was prepared by boiling 60 kg of *Morus alba* leaves in powder form with water at the ratio of 1:5, and evaporated to dryness using spray-dried apparatus. The percentage yield of the water extract was 18% w/w. The *Morus alba*-leaf extracts used in the

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TABLE 1. Effects of Morus alba-leaf extracts on glucose, glycosylated hemoglobin (HbA1c), total cholesterol and triglyceride levels in blood of 27 diabetic patients.

	Mean ± S.E.M.			
	Glucose (mg/dl)	Total Cholesterol (mg/dl)	Triglyceride (mg/dl)	HbA1c (%)
Baseline	155.11 ± 4.15	229.58 ± 11.24	235.38 ± 20.63	7.57 ± 0.22
Week 2	179.04 ± 9.26	211.24 ± 9.37	191.28 ± 15.96	
Week 4	173.62 ± 8.76	210.16 ± 9.92	174.52 ± 18.39	
Week 6	183.88 ± 9.50	204.48 ± 9.88	183.52 ± 21.58	
Week 8	185.84 ± 10.23	199.36 ± 10.10	168.24 ± 18.52	8.43 ± 0.23
P-value	0.004	<0.001	0.001	0.002

study were composed of 90% herb extracts and 10% maltodextrin. Each capsule of the study medication contained 350 mg of *Morus alba*-leaf extracts. The patient was instructed to take Morus alba-leaf extracts two capsules (700 mg) orally thrice daily before meals for eight weeks. Concomitant medications for diabetes or hyperlipidemia were not allowed during the study period.

Outcome measures

The patients were followed every two weeks for four visits. For each visit, the patient was asked for symptoms, examined by the investigators and had blood tests for complete blood count (CBC), fasting plasma glucose, total cholesterol, triglyceride, electrolytes, renal function, liver function as well as urine examination. Glycosylated hemoglobin assay was done at baseline and at the end of the study.

Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). Statistical comparisons between different values were done using paired student-t-test or repeated measured one-way analysis of variance (ANOVA). Significance was accepted at $P < 0.05$.

RESULTS

Twenty-seven patients with newly diagnosed type 2 diabete were included. Twenty-two patients were females. The mean age of the patients was 53.4 years. The patients' compliance to the study medication was satisfactory. The changes in fasting plasma glucose, glycosylated hemoglobin, blood total cholesterol and triglyceride are shown in Table 1. The mean fasting plasma glucose levels at baseline, week 2, week 4, week 6 and week 8 were 155.1, 179, 173.6, 183.9 and 185.8 mg/dl, respectively (p=0.04). The mean glycosylated hemoglobin levels at baseline and week 8 were 7.6% and 8.4%, respectively (p=0.002). The mean blood total cholesterol levels at baseline, week 2, week 4, week 6 and week 8 were 229.6, 211.2, 210.2, 204.5 and 199.4 mg/dl, respectively (p<0.001). The mean blood triglyceride levels at baseline, week 2, week 4, week 6 and week 8 were 235.4, 191.3, 174.5, 183.5 and 168.2 mg/dl, respectively (p=0.001). No patients experienced side effects of the treatment. Laboratory results on CBC, urine, blood electrolytes, renal function and liver function at baseline, week 2, week 4, week 6 and week 8 were not significantly different.

DISCUSSION

Our study was unable to detect hypoglycemic effect of *Morus alba*-leaf extracts at a dosage of 2.1 g per day for 8 weeks. Although *Morus alba* was found to have hypoglycemic effect in several animal studies,[6-8] one of these studies used *Morus alba* root bark extract.[8] Another animal study did not observe any hypoglycemic effect of *Morus alba*.[11] The hypoglycemic effect of higher dose of Morus alba-leaf extracts or the extracts from its root bark in patients with diabetes was unknown and needed further clinical study. It should be mentioned that the levels of fasting plasma glucose and glycosylated hemoglobin at the end of treatment were significantly higher than those at baseline. The reason for this observation was unclear. The study medication was composed of maltodextrin but this substance was not related to glucose. The amount of glucose in *Morus alba*-leaf extracts was minimal and this should not explain the increase in fasting plasma glucose at the end of treatment.

However our study showed that blood total cholesterol and triglyceride levels at the end of therapy were significantly reduced from those at baseline. The magnitude of the reductions was meaningful, i.e., blood total cholesterol level was reduced by 13% whereas blood triglyceride was reduced by 28.5%, and the mean blood levels of both total cholesterol and triglyceride at the end of therapy were less than 200 mg/dl. Our observation on lipid lowering effect of *Morus alba*-leaf extracts in the patients supported the findings from animal experiments.[9] Enkhmaa, et al. studied the effects of dietary consumption of *Morus alba* leaves and their major flavonol glycoside on the development of atherosclerotic lesions in LDL receptor-deficient mice. The mice fed with dried *Morus alba*-leaf powder or *Morus alba* leaves' major flavonol glycoside in addition to an atherogenic-diet for 8 weeks had significantly lower total cholesterol and triglyceride levels in the sera when compared with the control mice. Atherosclerotic lesion areas in *Morus alba*-treated mice were significantly reduced by 52% compared with that of the controls. Although a lipid lowering effect of *Morus alba*-leaf extracts in patients with type 2 diabetes observed in our study was very promising, the study was open-labeled without concurrent controls hence the effect could partly due to co-interventions. Although diet control instructions were not officially provided to the patients by the investigators during the study period, the patients might modify their eating habits due to a concern of having diabetes and this could lead to a reduction in blood lipids. Therefore, further clinical trials on treatment of patients with hyperlipidemia comparing *Morus alba*-leaf extracts to placebo or conventional lipid lowering agents are warranted.

CONCLUSION

The present study suggested that *Morus alba*-leaf extracts taken orally at a dosage of 700 mg thrice daily had no hypoglycemic effect but they exerted lipid lowering effect. Further clinical trials on treatment of patients with hyperlipidemia comparing *Morus alba*-leaf extracts to placebo or conventional lipid lowering agents are warranted.

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บทคัดย่อ

ประสิทธิผลและความปลอดภัยของใบหม่อน (Morus alba) ในการลดระดับน้ำตาลและไขมันในเลือดในผู้ป่วยเบาหวานชนิดไม่พึ่งอินสุลิน : การศึกษาเบื้องต้น

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คณะผู้วิจัยได้ศึกษาประสิทธิผลเบื้องต้นของสารสกัดใบหม่อนในการลดระดับน้ำตาลและไขมันในเลือดในผู้ป่วยเบาหวานชนิดไม่พึ่งอินสุลินรายใหม่จำนวน 27 คนที่ได้รับสารสกัดใบหม่อนด้วยน้ำขนาด 350 มิลลิกรัมบรรจุในแคปซูล รับประทานครั้งละ 2 แคปซูล วันละ 3 ครั้งก่อนอาหาร ติดต่อกันนาน 8 สัปดาห์ ผู้ป่วยทุกรายไม่ได้รับยารักษาเบาหวานหรือยาลดไขมันร่วมด้วย ระดับน้ำตาลในเลือดเฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 155.1, 179, 173.6, 183.9 and 185.8 มก/ดล. ตามลำดับ (p=0.004) ระดับ glycosylated hemoglobin เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 8 ภายหลังการรักษามีค่า 7.6% และ 8.4% ตามลำดับ (p=0.002) ระดับ total cholesterol เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 229.6, 211.2, 210.2, 204.5 และ 199.4 มก/ดล. ตามลำดับ (p<0.001) ระดับ triglyceride เฉลี่ยก่อนการรักษาและสัปดาห์ที่ 2, 4, 6 และ 8 ภายหลังการรักษามีค่า 235.4, 191.3, 174.5, 183.5 และ 168.2 มก/ดล. ตามลำดับ (p=0.001) ผู้ป่วยทุกรายไม่มีอาการข้างเคียงจากการรักษา สารสกัดใบหม่อน 2.1 กรัมต่อวันไม่สามารถลดระดับน้ำตาลในเลือดของผู้ป่วยเบาหวานได้ แต่อาจลดระดับไขมันในเลือดได้

Efficacy and Safety of Cinnamon Stomachic Mixture for Patients with Functional Dyspepsia

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ABSTRACT

Health care personnel at a community hospital have used cinnamon stomachic mixture for treatment of patients with functional dyspepsia for many years and they claimed that cinnamon stomachic mixture was effective without any supportive evidence.

Objective: To determine the efficacy, safety, patients' compliance and satisfaction with the treatment of cinnamon stomachic mixture.

Methods: This was a randomized controlled study in 318 adults with functional dyspepsia presenting to 6 community hospitals. The patients were randomized to receive 105 mg of simethicone three times a day or 30 ml of cinnamon stomachic mixture three times a day for 7 to 14 days. The patients were evaluated for improvement of symptoms, compliance to medication and patients' satisfaction with the treatment. The data were analysed by descriptive statistics, chi-square statistics, student t test, analysis of variance and non-parametric tests where appropriate.

Results: One hundred and fifty patients received simethicone and 168 patients received cinnamon stomachic mixture. The baseline characteristics of the patients in both groups were not significantly different. The patients' compliance to simethicone and cinnamon stomachic mixture was 82% and 89.3% respectively (p=0.09). The severity of the symptoms after treatment and the response rates were not significantly different between both groups. Side effects were observed in 9.3% and 9.5% in the simethicone group and the cinnamon stomachic mixture group respectively. Most of the patients in both groups were satisfied with the treatments they received. The cost of a 14-day course of cinnamon stomachic mixture was 36 baht compared with 84 baht for that of simethicone.

Conclusion: Cinnamon stomachic mixture is effective and safe for the treatment of the patients with functional dyspepsia similar to simethicone.

Keywords: Cinnamon stomachic mixture; functional dyspepsia; simethicone

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Dyspepsia refers to a group of upper gastrointestinal symptoms that occur commonly in adults. Dyspepsia is known to result from organic causes, but the majority of patients suffer from non-ulcer or functional dyspepsia.[1] The generally accepted definition by most clinicians includes the presence of upper abdominal pain or discomfort with or without other upper gastrointestinal symptoms, such as nausea, belching and vomiting. In studies using "upper abdominal pain" as the definition, the prevalence of uninvestigated dyspepsia has varied between 7%-34.2%.[1] Two recent randomized controlled trials revealed that simethicone was more effective than a placebo for the treatment of patients with functional dyspepsia and the response observed in the simethicone group was not significantly different from that in the cisapride

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TABLE 1. Baseline characteristics of the study patients.

Characteristic	Simethicone gr. (N=150)	Cinnamon stomachic mixture gr. (N=168)	P
Male : Female	45 : 105	44 : 124	0.53
Mean age, yr ± SD (Range)	48.6 ± 12.8 (19-80)	48.6 ± 13.3 (20-91)	0.99
Body weight, kg ± SD (Range)	57.8 ± 10.9 (35-97)	56.7 ± 13.3 (36-79)	0.2
Mean symptom score ± SD	53.7 ± 21.9	51.9 ± 19.5	0.36
Median symptom score	50	50	
Range of symptom score	20 - 100	15 - 100	

group.[2,3] The cinnamon stomachic mixture has been produced and used for the treatment of patients with functional dyspepsia at a community hospital (Uthong Hospital) in Thailand for many years. The health care providers at this community hospital claimed that most of the patients responded to cinnamon stomachic mixture and they were also satisfied with the treatment they received.

The objective of this study was to determine the efficacy and safety of cinnamon stomachic mixture for treatment of patients with functional dyspepsia.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of the Department of Development of Thai Traditional Medicine and Alternative Medicine, Ministry of Public Health. This was a randomized controlled study conducted in 6 community hospitals namely Uthong Hospital, Kudchum Hospital, Bangrathum Hospital, Wangchan Hospital, Soongnern hospital and Somdej-Prayuparap-Lerng-Nok-Ta Hospitals in Thailand. The eligibility criteria for the study subjects were 1) age 20 years, 2) symptoms of dyspepsia, 3) duration of symptoms between 3 days to 30 days and 4) agreed to participate in the study and signed the written informed consent form. The exclusion criteria were 1) pregnancy, 2) had symptoms suggestive of organic diseases i.e. fever, vomiting, hematemesis, melena, diarrhea, weight loss > 3 kilograms within a month and symptoms of other organic diseases, 3) had signs suggestive of organic diseases i.e. anemia, jaundice, hepatomegaly, splenomegaly, abdominal mass, signs of chronic liver diseases, ascites, abdominal tenderness or guarding, absence of bowel sounds, signs of intestinal obstruction and signs of other organic diseases, 4) had been taking ulcerogenic drugs e.g. aspirin, NSAIDS, and 5) allergic to simethicone or any components of cinnamon stomachic mixture.

The subjects were randomized to the simethicone group or the cinnamon stomachic mixture group by block randomization. The subjects in the simethicone group received simethicone tablet of 105 mg. 3 times daily for 7 to 14 days. The subject in the cinnamon stomachic mixture group received 30 ml of cinnamon stomachic mixture 3 times daily for 7 to 14 days. Each milliliter of cinnamon stomachic contained cinnamon bark *(Cinnamomum verum)*, "samunlawaeng" bark *(Cinnamomum bejolghota)*, licorice *(Glycyrrhiza glabra)* and clove *(Syzygium aromaticum)* at the amount equivalent to 7.14 mg of each crude drug.

The cinnamon stomachic mixture was produced by boiling 50 grams of dried cinnamon, samunlawaeng, licorice and dried clove in 7,000 ml of water for 15 minutes. Then a teaspoon of camphor and 70 ml of paraben were added after leaving such a solution at room temperature for 5 minutes. The preparation was left overnight and was distilled through a clean cloth before bottling the distilled solution in 300 ml glass bottles.

A sample size of 200 per group was estimated from the following information 1) the mean difference of the symptom score at baseline and at the end of treatment was 30 (from 60 to 30) in the simethicone group and 25 (from 60 to 35) in the cinnamon stomachic mixture group, 2) the standard deviation of the mean difference in the symptom score was 20, 3) type I error was 5%, and 4) type II error was 20%.

All subjects received instructions on eating habits and avoidance of the substances that might precipitate the dyspeptic symptoms. The subject was evaluated for dyspeptic symptoms at entry and day 7 and day 14 after treatment using a visual analog scale of 0 (no symptoms) to 100 (unbearable symptoms). Any concomitant or additional treatment, compliance to the study medications, new symptom and satisfaction with the study medication received including the convenience of taking medication, taste and odor of the medications were also recorded at follow up visits. The data were analyzed by descriptive statistics, chi square statistics, student t test, analysis of variance and non-parametric test where appropriate. The p value of < 0.05 was considered statistically significant.

RESULTS

There were 318 subjects, 150 in the simethicone group and 168 in the cinnamon stomachic mixture group. The baseline characteristics of the patients are shown in Table 1. Seventy percent of the patients were females. The mean age, mean body weight and mean symptom score of the patients in both groups were not significantly

TABLE 2. Treatment responses in terms of symptom score.

	Mean symptom score ± SEM		
	Simethicone gr. (N=150)	Cinnamon stomachic mixture gr. (N=168)	P
Before treatment	53.7 ± 1.8	51.9 ± 1.5	0.36
Day 7 after treatment	32.5 ± 1.6	29.3 ± 1.6	0.17
Day 14 after treatment	16.1 ± 1.5	15.5 ± 1.2	0.76
	p<0.001	p<0.001	

TABLE 3. Treatment responses in terms of disappearance of symptoms.

	Number of patients (%) with symptom score 10		
	Simethicone gr. (N=150)	Cinnamon Stomachic Mixture gr. (N=168)	P
Before treatment	0	0	
Day 7 after treatment	22 (14.7%)	36 (21.4%)	0.15
Day 14 after treatment	99 (66%) (95% CI 58.1% - 73.1%) p<0.001	106 (63.1%) (95% CI 55.6% - 70%) p<0.001	0.67

different. Concomitant treatments such as antacid were given to 20% and 11.9% of the patients in the simethicone group and the cinnamon stomachic mixture group respectively (p=0.07). A full compliance to the medications was reported in 82% and 89.3% of the patients in the simethicone group and the cinnamon stomachic mixture group respectively (p=0.09). The mean symptom scores at the baseline and those during and at the end of treatment are shown in Table 2. The mean symptom scores at the baseline in both groups were not significantly different (p=0.14). The mean symptom score on day 7 and day 14 was significantly less than that at the baseline in both groups (p<0.001). The mean symptom scores on day 7 and day 14 in both groups were not significantly different. The treatment responses in terms of disappearance of symptoms (symptom score 10) are shown in Table 3. The response rates on day 7 and day 14 were significantly greater than those at the baseline in both groups (p<0.001). The response rates on day 7 and day 14 in both groups were not significantly different. Side effects were observed in 9.3% and 9.5% in the simethicone group and the cinnamon stomachic mixture group respectively. The common side effects were nausea, eructation, air discharge from the anus, dizziness and constipation. All side effects were mild and no medication-related serious adverse events were observed. Most of the patients in both groups were satisfied with the treatments they received i.e. 80% and 83.3% of the patients in the simethicone group and the cinnamon stomachic mixture group indicated that they would like to receive the same treatments if they had the same symptoms.

DISCUSSION

The Gastroenterological Association of Thailand reported that the prevalence of dyspepsia in Thais was 20% to 25% and the incidence of dyspepsia in Thais was 1% to 2%. A significant proportion of dyspeptic patients were functional dyspepsia cases. Therefore functional dyspepsia is one of the very common health problems in Thailand and it consumes a large amount of health care resources. A meta-analysis on psychological interventions for non-ulcer dyspepsia concluded that there was insufficient evidence to confirm the efficacy of psychological intervention in non-ulcer dyspepsia.[4] Another meta-analysis on pharmacological interventions for non-ulcer dyspepsia revealed that prokinetics, H2 receptor antagonists and proton pump inhibitors were effective in therapy of non-ulcer dyspepsia.[5] These effective medications are expensive and have side effects. Many herbal medicines were found to be effective for treatment of functional dyspepsia. They were ganaton, extracts from bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root & lemon balm, artichoke leaf extract, iberogast, peppermint oil & caraway oil and red pepper.[6-12] However there has been no study on the efficacy and safety of cinnamon stomachic mixture for treatment of functional dyspepsia.

We conducted this randomized controlled study in 6 community hospitals where sophisticated investigations such as gastroscopic examination and urea breath test were unavailable and we needed to enroll the subjects diagnosed as having functional dyspepsia based on their clinical features. Simethicone was chosen as a comparator drug instead of placebo because there was evidence that simethicone was more effective than a placebo in treating functional dyspepsia[2,3]. Simethicone was also the medication most commonly used by health care personnel at these community hospitals for treating the patients with functional dyspepsia. We did not use cisapride in our study although it was a prokinetic drug because cisapride has many drug interactions leading to serious side effects and it is no longer a treatment option in functional dyspepsia.[13,14]

Our study found that cinnamon stomachic mixture was effective in alleviating the symptoms by 70% and had a favorable response of 63% at the end of 2 weeks, similar to that of simethicone. The use of cinnamon stomachic mixture for longer duration might increase the response rate since many clinical studies on the treatment of functional dyspepsia used the study medications for longer than 4 weeks[2, 3, 9, 12, 15-17] and they found a favorable response of up to 80%. However, we did not use a longer duration of treatment since we thought that the patients who did not respond to a 2-week course of medication should have further appropriate investigations performed to detect organic causes of their persistent dyspeptic symptoms. The side effects of cinnamon stomachic mixture were uncommon and all of them had mild severity. The patients who received cinnamon stomachic mixture showed a very good compliance to treatment and were satisfied with this treatment. Moreover the cost of a 14-day course of cinnamon stomachic mixture was 36 baht compared with 84 baht for that of simethicone.

In summary cinnamon stomachic mixture for 2 weeks is effective, safe and cheap in relieving the symptoms of 60% of the patients with a clinical diagnosis of functional dyspepsia and it should be included as a treatment option for functional dyspepsia, especially in community hospitals.

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บทคัดย่อ

ประสิทธิผลและความปลอดภัยของยาธาตุอบเชยในการรักษาผู้ป่วย Functional Dyspepsia

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บุคลากรการแพทย์ที่ปฏิบัติงานที่โรงพยาบาลชุมชนรักษาผู้ป่วย functional dyspepsia ด้วยยาธาตุอบเชยพบว่าผู้ป่วยส่วนมากมีอาการทุเลาหรืออาการหายไป แต่ยังไม่มีการวิจัยทางคลินิกเพื่อประเมินประสิทธิผลและความปลอดภัยของยาธาตุอบเชยตำรับนี้

วัตถุประสงค์: เพื่อทราบประสิทธิผล ความปลอดภัยของการรักษาผู้ป่วย functional dyspepsia ด้วยยาธาตุอบเชย

วิธีการ: การวิจัยนี้ใช้รูปแบบ Randomized controlled study ดำเนินการที่โรงพยาบาลชุมชน 6 แห่งในผู้ใหญ่ที่ได้รับการวินิจฉัยโดยอาศัยลักษณะทางคลินิกว่าเป็น functional dyspepsia จำนวน 318 คน ผู้ป่วยถูกสุ่มให้ได้รับ simethicone ขนาด 105 มก รับประทานวันละ 3 ครั้งหลังอาหาร หรือยาธาตุอบเชยรับประทานครั้งละ 30 มล วันละ 3 ครั้งหลังอาหารติดต่อกันนาน 7-14 วัน ผู้ป่วยได้รับการประเมินผลการรักษาภายหลังการรักษานาน 7 วัน และ 14 วัน โดยประเมินอาการทั้งหมดของผู้ป่วย ความสม่ำเสมอของการรับประทานยาที่ได้รับ ผลข้างเคียงของการรักษา และความพึงพอใจของผู้ป่วยต่อการรักษาที่ได้รับ นำข้อมูลมาวิเคราะห์ด้วยสถิติเชิงพรรณนา, chi-square statistics, student t test หรือ analysis of variance หรือ non-parametric test

ผลการศึกษา: ผู้ป่วย 150 คนได้รับ simethicone และผู้ป่วย 168 คนได้รับยาธาตุอบเชย ลักษณะทั่วไปของผู้ป่วยทั้ง 2 กลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญ ผู้ป่วยร้อยละ 82 ในกลุ่ม simethicone และร้อยละ 89.3 ในกลุ่มยาธาตุอบเชย (p=0.09) รับประทานยาครบทุกมื้อ อาการของผู้ป่วยและความรุนแรงเฉลี่ยอาการของผู้ป่วยภายหลังการรักษาด้วย simethicone หรือยาธาตุอบเชยไม่แตกต่างกันอย่างมีนัยสำคัญ จำนวนผู้ป่วยที่อาการดีขึ้นมากหรืออาการหายไปภายหลังการรักษาด้วย simethicone หรือยาธาตุอบเชยเพิ่มขึ้นจากก่อนการรักษาอย่างมีนัยสำคัญ และจำนวนผู้ป่วยที่อาการดีขึ้นมากหรืออาการหายไปภายหลังการรักษาด้วย simethicone หรือยาธาตุอบเชยไม่แตกต่างกันอย่างมีนัยสำคัญ ผลข้างเคียงของการรักษาพบร้อยละ 9.3 ในกลุ่ม simethicone และร้อยละ 9.5 ในกลุ่มยาธาตุอบเชย และผู้ป่วยส่วนมากที่ได้รับ simethicone หรือได้รับยาธาตุอบเชยพึงพอใจต่อการรักษาที่ได้รับไม่แตกต่างกัน ค่าใช้จ่ายของยาธาตุอบเชยประมาณ 36 บาท ส่วนค่าใช้จ่ายของ simethicone ประมาณ 84 บาท

สรุป: ยาธาตุอบเชยรับประทานติดต่อกัน 14 วันมีประสิทธิผลและปลอดภัยในการรักษาผู้ป่วย functional dyspepsia ไม่แตกต่างจากการรักษาด้วย simethicone

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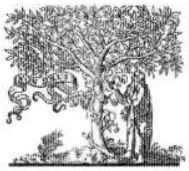

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Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Siriraj Hospital, Bangkok, Thailand

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Summary
Objective: To determine the efficacy and safety of colistin (colistimethate sodium) produced by a local pharmaceutical company in Thailand for the treatment of infections caused by multidrug-resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
Methods: Patients hospitalized at Siriraj Hospital between January 2005 and April 2006, who had infections caused by MDR *P. aeruginosa* or *A. baumannii*, were enrolled in the study. Colistin (colistimethate sodium) at a dosage of 5 mg/kg/day was given intravenously in two divided doses. Primary outcomes were the clinical response and 30-day mortality; secondary outcomes were microbiological response and adverse events.
Results: Ninety-three patients infected with MDR *P. aeruginosa* and *A. baumannii* were enrolled. Seventy-eight patients (71 with *A. baumannii* and seven with *P. aeruginosa*) received colistin, whereas 15 patients (12 with *A. baumannii* and three with *P. aeruginosa*) received other antibiotics. The mean age, gender, underlying conditions and severity of illness of the patients in both groups were not significantly different. In the colistin group, 63 patients (80.8%) had a favorable clinical response and 94.9% had a microbiological response. The overall mortality of the patients in the colistin group was 46.2% and that in the non-colistin group was 80%. Nephrotoxicity was found in 24 patients (30.8%) in the colistin group and 17 of them had predisposing factors contributing to their renal dysfunction. No neurotoxicity was observed among the 78 patients.

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Conclusion: Locally produced colistin appears to be safe and effective for the treatment of infections caused by MDR *P. aeruginosa* and *A. baumannii* in Thai adult patients.

Introduction

Nosocomial infections caused by multidrug-resistant (MDR) organisms are emerging worldwide.[1–3] The incidence of MDR pathogens, particularly *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, in Thailand has dramatically increased.[4] A prospective cohort study of 208 clinical isolates of *A. baumannii* recovered from the patients in Siriraj Hospital from January to December 2002, revealed that 86 strains (41.3%) were isolated from the infected patients and the remaining 58.7% were colonizers.[5] In this study, 57% of *A. baumannii* isolates were resistant to all antimicrobial agents available in Thailand including beta-lactams, aminoglycosides and fluoroquinolones, and the overall mortality rate of the patients infected with pandrug-resistant *A. baumannii* was 79%.[5] The study of 104 clinical isolates of *A. baumannii* from 100 hospitalized patients at Maharaj Nakorn Chiang Mai hospital, Thailand also observed that 46% of the isolates were pandrug-resistant and the overall mortality was 52%.[6]

Over the past few years there have been reports on treating patients infected with MDR *A. baumannii* and *P. aeruginosa* with polymyxin B and colistin.[7–9] They found that polymyxin B and colistin had modest efficacy and were safe. In vitro activity of polymyxin B and colistin against 100 clinical isolates of MDR *A. baumannii* and 100 isolates of *P. aeruginosa* collected from the patients hospitalized at Siriraj Hospital from 2002 and 2003, revealed that all isolates were susceptible to polymyxin B and colistin.[10] However polymyxins are not available in Thailand and international pharmaceutical companies do not have a policy to import polymyxins to Thailand. Therefore we asked a local pharmaceutical company to produce colistin and this product has been approved by the Thai Food and Drug Administration since 2004.

The objective of this study was to determine the efficacy and safety of colistin produced by a local pharmaceutical company in Thailand for the treatment of infections caused by MDR *P. aeruginosa* and *A. baumannii*.

Methods

The study was approved by the ethics committee on human research of the Faculty of Medicine Siriraj Hospital, and all participating subjects signed the informed consent form. This was a pragmatic clinical trial conducted at Siriraj Hospital, Bangkok, Thailand, between January 2005 and April 2006. The eligible subjects were hospitalized patients over the age of 18 years who were infected with *A. baumannii* or *P. aeruginosa* resistant to beta-lactams, fluoroquinolones and aminoglycosides. We excluded patients with infections caused by *A. baumannii* or *P. aeruginosa* with other bacteria from our study because we felt that it was difficult to determine the efficacy of colistin for treatment of infections caused by MDR *A. baumannii* or *P. aeruginosa*. Colistin was offered to all such patients and if the patients and their responsible physicians agreed to have colistin treatment, the patients received intravenous colistin (colistimethate sodium) of 5 mg/kg/day in two divided doses. The dosage of colistin was adjusted according to the patients' renal function.[11] If the patients or their responsible physicians did not wish to join the study, they received other antibiotics according to their physicians' decisions and these patients were defined as the 'non-colistin group'.

All isolates of *A. baumannii* and *P. aeruginosa* from the eligible patients were tested for colistin susceptibility by E-test according to the manufacturer's guidelines (AB Biodisk, Sweden). A suspension of each isolate in Mueller–Hinton broth (BBL-Becton Dickinson, USA), adjusted to the density of a 0.5 McFarland standard, was swabbed in three directions to ensure uniform growth onto Mueller–Hinton agar (BBL-Becton Dickinson, USA) plates. Once the agar surface was completely dry, an E-test colistin strip (ranging from 0.06 to 1024 μg/ml) was applied to each plate and the plates were incubated at 35 °C for 16–20 hours. The minimum inhibitory concentration (MIC) was read where inhibition of growth intersected the E-test strip. Quality control strains of *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used with the reference MIC range of 0.125–0.5 and 0.5–2 mg/l, respectively. The susceptible isolate was defined as having a MIC of $\leq$2 mg/l. Quantitative colistin serum level was determined by microbiological assay.[12]

The primary outcomes were the clinical response and 30-day mortality. A good clinical response referred to a combination of clinical cure and clinical improvement. Clinical cure was defined as a disappearance of symptoms and signs of infection and clinical improvement was defined as a partial resolution of the symptoms and signs of infection. The secondary outcomes were microbiological response and adverse effects. Successful microbiological response was defined as an eradication of the causative organisms at the end of treatment. Nephrotoxicity was defined as an increase in serum creatinine of at least two-fold of the baseline value or a 30% decrease of creatinine clearance from the baseline value.

Results

Between January 2005 and April 2006, 93 patients met the inclusion criteria. Seventy-eight patients were in the colistin group and 15 patients in the non-colistin group. The baseline characteristics of the patients are shown in Table 1. The mean age, gender, underlying conditions, and severity of illness of the patients in both groups were not significantly different.

Presenting infections in the colistin group were: pneumonia (54), bacteremia and/or catheter related infection (9), intra-abdominal infection (5), urinary tract infection (4), skin and soft tissue infection (5), and sinusitis (1). In the colistin group, 71 patients (91%) were infected with *A. baumannii* and

Table 1 Baseline characteristics of the patients

Characteristic	Colistin group ($N = 78$)	Non-colistin group ($N = 15$)
Male	45 (57.7%)	11 (73.3%)
Mean age, years (range)	63.5 (18–103)	58.9 (27–90)
ICU admission	45 (57.7%)	5 (33.3%)
Mechanical ventilation	62 (79.5%)	14 (93.3%)
Mean APACHE II score	21.9	22.3
Pre-existing renal impairment (serum creatinine ≥1.5 mg/dl)	37.2%	40%
Pathogenic organism		
Acinetobacter baumannii	71 (91.0%)	12 (80%)
Pseudomonas aeruginosa	7 (9.0%)	3 (20%)
Underlying condition		
Diabetes mellitus with or without other medical conditions	16 (20.5%)	1 (6.7%)
Cardiovascular diseases	3 (3.9%)	3 (20%)
Cancers	6 (7.7%)	1 (6.7%)
Immunosuppressive treatment	4 (5.1%)	–
Cerebrovascular diseases	7 (9.0%)	–
Chronic obstructive pulmonary disease	7 (9.0%)	–
Other chronic medical conditions	12 (15.4%)	4 (26.7%)
Traumatic surgical patients	10 (12.8%)	4 (26.7%)
Recent cardiovascular surgery	8 (10.3%)	2 (13.3%)
Recent brain surgery	4 (5.1%)	–
Recent abdominal surgery	1 (1.3%)	–

seven (9%) were infected with *P. aeruginosa*, whereas 12 patients (80%) were infected with *A. baumannii* and three (20%) were infected with *P. aeruginosa* in the non-colistin group. In vitro susceptibility tests determined by E-test revealed that all *A. baumannii* and *P. aeruginosa* isolates had a MIC of colistin less than 2 mg/l and were considered susceptible to colistin. In the colistin group, 33 patients (42.3%) received colistin alone, whereas 45 patients (57.7%) received colistin with other antibiotics including vancomycin, aminoglycosides, metronidazole or carbapenems. In the non-colistin group, the patients received carbapenems (6), cefoperazone/sulbactam (3), cefoperazone/sulbactam combined with netilmicin (4), and cefoperazone/sulbactam combined with carbapenem (2).

The treatment outcomes are shown in Table 2. Sixty-four patients (82.1%) in the colistin group had a good clinical response. The clinical response in the patients who received colistin alone was 84.8% and in those who received colistin with other antibiotics was 77.8%; only four patients (26.7%) in the non-colistin group responded.

All cause mortality within 30 days was 46.2% in the colistin group and 80% in the non-colistin group ($p = 0.03$). The relative risk of death in the colistin group was 0.58 of the non-colistin group with a 95% confidence interval (CI) of 0.41 to 0.82. The difference in mortality was statistically significant and the number needed to treat (NNT) was approximately three, which implies that only three patients infected with MDR *A. baumannii* or *P. aeruginosa* needed to be treated with colistin in order to prevent one additional death. The overall mortality rates of the patients infected with *A. baumannii* and *P. aeruginosa* in the colistin group were 46.5% and 42.9%, respectively.

A microbiological response was found in 94.9% of the patients in the colistin group and none in the non-colistin group. Nephrotoxicity was observed in 24 patients (30.8%) in the colistin group. The incidence of nephrotoxicity of the patients in the colistin group was significantly less than that in the non-colistin group. Seventeen (70.8%) of 24 patients in the colistin group who developed nephrotoxicity had other predisposing factors contributing to a decline in renal function including nephrotoxic drugs, chronic kidney diseases, and hypovolemia. Nephrotoxic effects were mild and reversible without requiring renal replacement therapy. No neurotoxicity or drug reaction was observed in the patients who received colistin. The average dose of colistin was 179.6 mg/day, the average duration of colistin treatment was 11.9 days, and the average total dose of colistin was 2.1 g/patient/course.

Table 2 Treatment outcomes of the patients

Outcome	Colistin group ($N = 78$)	Non-colistin group ($N = 15$)	p Value
Good clinical response	63 (80.8%)	4 (26.7%)	<0.001
All cause mortality within 30 days	36 (46.2%)	12 (80%)	0.03
Microbiological response	74 (94.9%)	0	<0.001
Nephrotoxicity	24 (30.8%)	10 (66.7%)	0.02
Neurotoxicity	0	0	

Discussion

This study used colistimethate sodium (also called colistin methanesulfate, pentasodium colistimethane sulfate, or colistin sulfonyl methate), which is less potent and less toxic than colistin sulfate.[13,14] Colistin has a narrow spectrum of antimicrobial activity and is active against most aerobic Gram-negative bacilli including *P. aeruginosa* and *Acinetobacter spp*, even the organisms that are multidrug-resistant.[13] Several reports published during the period 1999 to 2003 revealed that polymyxins were effective and safe for treatment of patients infected with MDR Gram-negative bacteria including *A. baumannii* and *P. aeruginosa*.[7–9] We therefore attempted to study the efficacy and safety of locally produced colistin.

We were unable to do a randomized controlled study to compare colistin with other antibiotics since it would be unethical to provide antibiotics likely to be ineffective to patients, while the antibiotic active against the causative pathogens, colistin, was available. Therefore we had to offer colistin to all patients who had infections caused by *A. baumannii* or *P. aeruginosa* resistant to beta-lactams, fluoroquinolones and aminoglycosides. However, the baseline characteristics of the patients including mean age, gender, underlying conditions, severity of illness and the sites of infections of the patients in both groups were comparable.

The results from our study also showed a good clinical outcome and less overall mortality in patients who received colistin for treatment of MDR *A. baumannii* and *P. aeruginosa*. A good clinical outcome was found in 82.1% of patients treated with colistin no matter how the patients received it, alone or with other antibiotics. Overall mortality decreased from 79% in a previous study of *A. baumannii* infections in the same hospital to 46.5% of the patients infected with *A. baumannii* treated with colistin in this study.[5] The overall mortality in the non-colistin group in this study was still up to 80%. Furthermore, NNT for mortality from our study was only three, indicating that only three patients infected with MDR *A. baumannii* or *P. aeruginosa* needed to be treated with colistin in order to prevent one additional death. Moreover the cost of colistin was approximately 10 to 20 times lower than that of other antibiotics used to treat MDR *A. baumannii* and *P. aeruginosa* such as carbapenems, cefoperazone/sulbactam, and cephalosporins with or without aminoglycosides.

A microbiological response was observed in 74 patients (94.9%) in the colistin group. Three patients who did not have a microbiological response also had a good clinical outcome. However, antibiotic susceptibility profiles of these persistent isolates were different from those of the original isolates and these isolates could be new colonizers. In four patients who had no microbiological response after 72 hours of colistin treatment, the serum levels of colistin were measured by bioassay and the results showed that colistin levels were adequate at 4–8 times above the MIC of the organism. Therefore the same dose of colistin was continued for 7 days and all patients eventually had a microbiological response. We excluded patients with infections caused by *A. baumannii* or *P. aeruginosa* with other bacteria from our study, therefore the efficacy of colistin for treatment of mixed infections is unknown.

Nephrotoxicity is an important side effect of colistin. In our study, nephrotoxicity was found in 30.8% of the patients receiving colistin; this is comparable to the results found in a previous report.[15] Some patients in the colistin group who developed nephrotoxicity also had other contributing factors. Nephrotoxicity in these patients was mild and reversible without requiring renal replacement therapy. Some patients had improvement in their renal function after colistin treatment, which implies that the worsening of renal function was probably due to a severe infection or other conditions. The incidence of nephrotoxicity of the patients in the non-colistin group was significantly more than that in the colistin group. This observation might be due to uncontrolled infections and the side effects of medications including antibiotics given to the patients. No neurotoxicity or drug reaction was observed in the patients in our series.

Although the ability of Gram-negative bacteria to develop resistance to colistin is rare, such Gram-negative bacteria can develop resistance to colistin through mutation or adaptation mechanisms.[13,16] We therefore recommend that colistin, as the only currently available drug for the treatment of MDR Gram-negative bacteria in Thailand, should be reserved for treatment of infections caused by multidrug-resistant Gram-negative bacteria that are only susceptible to colistin.

In summary, we found that colistin appears to be safe and effective for treatment of infections caused by multidrug-resistant *P. aeruginosa* and *A. baumannii* in Thai adult patients. Treatment with colistin decreases patient mortality and is cost-effective.

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