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Research Article

The impact of antimicrobial stewardship on appropriate use of antimicrobial agents for nosocomial infections caused by gram-negative bacilli in a university hospital in Thailand

Sang Usayaporn[1], Terapong Tantawichien[2], Preecha Montakantikul[3*]

[1] Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand
[2] Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[3] Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

ABSTRACT

Antimicrobial stewardship programs (ASP) are crucial for promoting appropriate antimicrobial use and combatting resistance. This prospective cohort study evaluated the impact of ASP on the appropriate use of antimicrobial agents in a university hospital. This study was conducted over a 6-month period, comparing the outcomes of patients managed under the ASP with those in a control group. The primary objective was to assess the appropriate use of antimicrobials. Secondary outcomes included de-escalation rate, duration of therapy, and clinical outcomes (infection-related mortality, clinical and microbiological cure). A total of 311 patients were enrolled in the study, with 181 in the ASP ward and 130 in the control ward. Baseline characteristics were generally comparable between the two groups, except for a lower median age in the ASP group. The appropriateness of antimicrobial use did not significantly differ between the ASP and control groups (67.96% vs. 68.46%, P=0.925). However, the ASP group showed a higher rate of de-escalation (43.09% vs. 23.85%, P<0.01) and a shorter duration of antimicrobial therapy (8 vs. 10 days, P=0.031). Importantly, clinical cure rate was higher in the ASP ward (83.43% vs. 67.69%, P=0.01). There were no significant differences in infection-related mortality and microbiological cure between the two groups. The ASP implementation in a university hospital resulted in increased rates of de-escalation and shorter durations of antimicrobial therapy while the overall appropriate use did not significantly improve. These findings highlight the potential benefits of ASP in optimizing antimicrobial treatment without compromising clinical outcomes.

Keywords:
Antimicrobial stewardship programs, Appropriateness of antimicrobial use, De-escalation, Duration of therapy, Clinical outcomes

1. INTRODUCTION

The development of antimicrobial agents has declined over the past 20 years, while antimicrobial resistance has been increasing. As a result, treating multidrug-resistant organisms has become challenging. This situation highlights the urgent need for new antimicrobial agents with novel mechanisms to combat the emergence of resistant pathogens[1]. Unfortunately, there are only a few new antimicrobial agents in the pharmaceutical development pipeline specifically targeting gram-negative resistant bacteria. It is well-known that inappropriate antimicrobial use is a significant contributor to the development of antimicrobial resistance. Therefore, it is crucial to employ several methods to ensure the judicious use of available antimicrobials. Additionally, implementing an effective infectious control program alongside the appropriate use of antimicrobial agents is essential in combating antimicrobial resistance[2].

Antimicrobial stewardship programs (ASP) aim to improve patient outcomes and optimize the use of antimicrobials. The guidelines for ASP, developed by the

***Corresponding author:**
*Preecha Montakantikul Email: preecha.mon@mahidol.ac.th

Infectious Diseases Society of America (IDSA), outline various strategies to promote the optimal use of antimicrobials[3-4]. Numerous studies have provided evidence demonstrating the effectiveness of ASPs in reducing antimicrobial consumption[5-7] and the incidence of infections caused by multidrug-resistant gram-negative bacteria, as well as the colonization with antimicrobial-resistant bacteria and *Clostridium difficile* infections[8].

Antimicrobial resistance among gram-negative bacteria poses a significant challenge in Thailand. Extensively drug-resistant *Acinetobacter baumannii* complex and carbapenem-resistant *Klebsiella pneumoniae* are prevalent, accounting for 41.9% and 17.2%, respectively, across 47 hospitals in the country[9]. To address this issue, it becomes imperative to ensure the appropriate use of currently available antimicrobials. However, there is limited data and insufficient studies assessing the outcomes of antimicrobial stewardship programs in Thailand. Therefore, the objective of this study was to assess the impact of an ASP on the appropriate use of antimicrobial agents for nosocomial infections caused by gram-negative bacilli. The study aims to evaluate the effectiveness of the ASP in improving the rational use of antimicrobial agents, considering the specific challenges posed by antimicrobial resistance in Thailand.

2. MATERIALS AND METHODS

2.1. Study design

This study was an observational prospective cohort comparative study, conducted at King Chulalongkorn Memorial Hospital in Bangkok, Thailand. It aimed to compare the impact of an antimicrobial stewardship program (ASP) implemented in a medicine ward with another ward that did not have any similar programs.

2.2. Interventions

The study was conducted over a 6-month period, specifically from September 2015 to February 2016. During this time, eligible patients admitted to two medical wards and receiving antimicrobial agents for the treatment of nosocomial infections were included in the study. In one unit, referred to as the study unit, an antimicrobial stewardship program (ASP) was implemented. This unit consisted of a 30-bed medicine ward. The other unit, called the control unit, served as the control group, and did not have any antibiotic control programs in place. It was a 20-bed medicine ward.

The ASP strategy employed in the study unit focused on the empirical antimicrobial treatment of nosocomial infections. In contrast, in the control unit, patients with suspected nosocomial infections received empirical antimicrobial treatment prescribed by rotating residents under the supervision of attending physicians. The ASP approach utilized a range of interventions and strategies, with the core strategy being a prospective audit with intervention and feedback. Additionally, an education program was provided to the prescribers, drug use evaluation was conducted, dose optimization and de-escalation therapy were emphasized, and collaboration with an infection control program was established. The ASP was led by a multidisciplinary team consisting of an infectious diseases training pharmacist, two infectious diseases physicians, and an infection control nurse. Patients who received antimicrobial agents in the study unit were regularly evaluated through daily rounds and chart reviews conducted by the study team. The team members actively intervened in prescribing decisions related to the treatment of suspected or proven bacterial infections. Furthermore, the ASP team held monthly meetings to discuss their findings and optimize antimicrobial management strategies.

2.3. Patient population

The study included patients who were 18 years of age or older and were admitted to the study and control wards for a duration of more than 48 hours during the study period. These patients met the eligibility criteria for participation in the study. This study included all patients who were diagnosed with nosocomial infections or suspected of having healthcare-associated infections. Eligible patients were those who received any of the following antimicrobial agents, namely imipenem/cilastatin, meropenem, doripenem, piperacillin/tazobactam, ceftazidime, cefoperazone/sulbactam, cefepime, ciprofloxacin, and levofloxacin, for empirical treatment. Patients with a history of allergy to any of the antimicrobial agents included in the study or those who were unable to receive any antimicrobials were excluded from participation.

2.4. Data collection and data analysis

The study prospectively collected various data for all patients, including their age, gender, underlying diseases, empirical and documented antimicrobial use, dosage and regimens, duration of treatment, diagnosis upon admission, site of infections, microbiology results, and clinical outcomes. These clinical outcomes encompassed infection-related mortality, clinical cure, and microbiological cure.

2.4.1. Primary outcome

The data analysis focused on evaluating the rate of appropriateness of antimicrobial use for empirical treatment of nosocomial infections. The assessment was based on indications documented in the drug use evaluation forms, which were approved by the infectious disease unit and aligned with the institutional guidelines. The forms served as a tool to evaluate and ensure the appropriate use of antimicrobial agents in the treatment of nosocomial infections. The analysis aimed to determine the extent to which antimicrobial treatment aligned with the recommended indications and guidelines.

2.4.2. Secondary outcomes

De-escalation rate and duration of treatment: The study evaluated the rate of de-escalation and duration of antimicrobial treatment. De-escalation refers to the adjustment of therapy to a narrower-spectrum or more targeted antimicrobial agent based on clinical and microbiological data. Additionally, the discontinuation of antimicrobial therapy, when clinical and microbiological data did not support the presence of a bacterial infection, was included in the calculation of the de-escalation rate.

Clinical outcomes: The study assessed several clinical outcomes, including infection-related mortality, clinical improvement (both clinical cure and microbiological cure). Clinical cure refers to the resolution or improvement of the infection without the need for additional antimicrobial therapy and microbiological cure refers to the achievement of at least one negative culture of a pathogen that was obtained during or after the course of antimicrobial therapy. These outcomes were used to evaluate the effectiveness of the antimicrobial treatment in resolving the nosocomial infections.

2.5. Statistical analysis

For comparing the rate of appropriateness empirical antimicrobial use, de-escalation rate and duration of treatment, as well as clinical outcomes, statistical analysis was employed. Categorical variables were assessed using either the chi-square test or Fisher's exact test, while continuous variables were analyzed using the Mann-Whitney U test. All data analyses were conducted using SPSS software, specifically version 22.

3. RESULTS

During the study period, a total of 652 patients were admitted to the study unit, while 368 patients were admitted to the control unit. Out of these, 311 patients met the eligibility criteria for inclusion in the study. Specifically, 181 patients were admitted to the study ward, and 130 patients were admitted to the control ward. Please refer to Figure 1 for a graphical representation of these numbers.

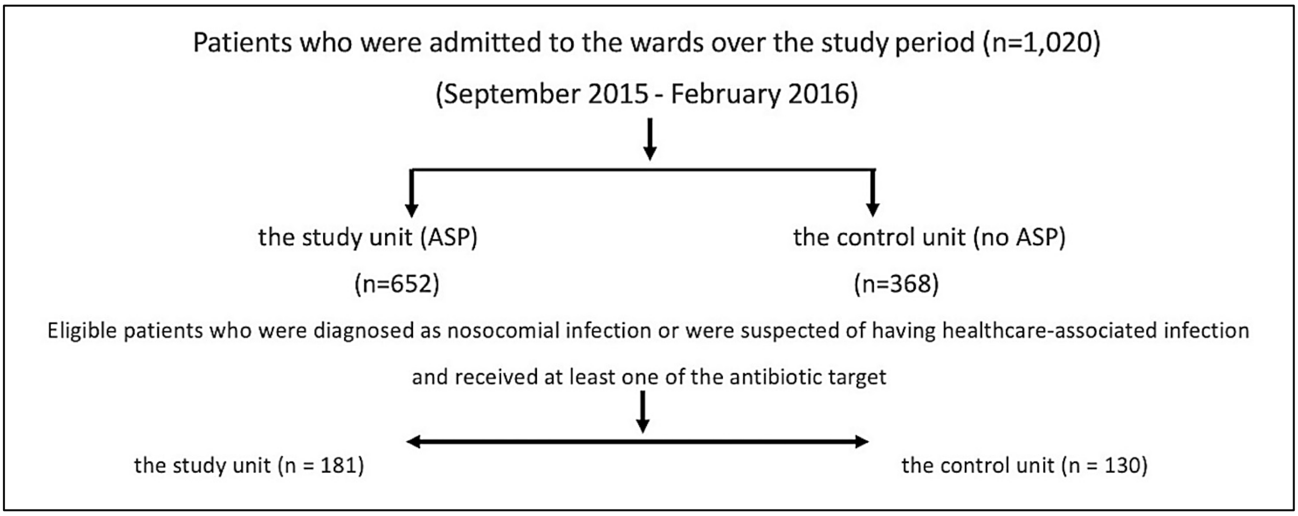

Figure 1. Flow diagram of the study participants.

3.1. Baseline characteristics

Most baseline characteristics were comparable between the study and control groups, with the exception of a lower median age and a small number of male patients and patients with liver cirrhosis in the study group. The median age of the study patients was 68 years (interquartile range [IQR]: 54.5-81), while the median age of the control group was 75 years (IQR: 69-84.25). The baseline characteristics of the patients are summarized in Table 1.

Furthermore, there were no significant differences between the two groups in terms of the gram-negative bacteria isolated from the patients. The rate of multidrug-resistant pathogens isolated was also similar in both wards. Detailed microbiology results from the patients can be found in Table 2.

3.2. Primary and secondary outcomes

The rate of appropriateness of antimicrobial use did not show a significant difference between the study ward (67.96%) and the control ward (68.46%) (P=0.925). However, the de-escalation rate was significantly higher in the study ward compared to the control ward (43.09% vs. 23.85%, P<0.01). Additionally, the median duration

Table 1. Baseline characteristics of the patients.

Baseline characteristics	**Study ward (%)**	**Control ward (%)**	***P*-value**
Number of patients	181	130	
Median Age (years, IQR)	68 (54.5-81)	75 (69-84.25)	<0.010*
Males	51.93	73.85	<0.010*
Comorbidities	98.90	100.00	0.512
- Diabetes	34.81	40.77	0.284
- Chronic Kidney Disease	23.20	29.23	0.230
- Cirrhosis	3.87	10.00	0.030*
- Heart failure	10.50	8.46	0.549
- Immunocompromised#	42.54	40.77	0.755
Hospitalization within 90 days	39.78	39.23	0.922
Prior antimicrobial therapy in the past 90 days	57.46	57.69	0.967
Empirical treatment	93.92	90.77	0.295
Definitive treatment	6.08	9.23	0.230
Site of infections or diagnostic			0.238
- Lower respiratory tract infections or	30.94	32.31	
- Urinary tract infections	29.83	24.62	
- Intra-abdominal infections	13.81	17.69	
- Skin and soft tissue infections	6.63	3.85	
- Febrile neutropenia	5.52	1.54	
- Catheter-related blood stream infection	1.10	2.31	
- Others$	12.15	17.69	
Bacteremia	5.52	2.31	0.162
Sepsis or septic shock	15.47	20.77	0.227

#human immunodeficiency virus (HIV) infection, received immunosuppressives, chemotherapy, cancer, neutropenic patients and hematologic malignancy
$Others = upper respiratory tract infections, diarrhea, tuberculosis, pressure sore
*P<0.05

Table 2. Microbiology results from the participants.

	Study unit % (n = 89)	**Control unit % (n = 70)**	***P*-value**
Microbiology results			0.884
Pseudomonas aeruginosa	12.36	14.29	
Acinetobacter baumannii	13.48	8.57	
Enterobacterales	58.43	61.43	
Gram-positive bacteria	13.48	14.29	
Others$	2.25	1.43	
Multidrug resistant pathogens	36.59	35.29	0.87
Extensively drug resistant pathogens	2.44	2.94	1.00

$Others = *Stenotrophomonas maltophilia* (n=2), *Mycobacterium avium* complex (n=1)

Table 3. Primary and secondary outcomes analysis.

Outcomes	**Study unit (n=181)**	**Control unit (n=130)**	***P*-value**
Appropriate antimicrobial use (%)	67.96	68.46	0.925
De-escalation rate (%)	43.09	23.85	<0.010*
Median duration of antimicrobial use (days, IQR)	8 (5-14)	10 (7-14)	0.031*

*P<0.05

Table 4. Clinical outcomes.

Clinical outcomes	**Study unit % (n)**	**Control unit % (n)**	***P*-value**
Infection-related mortality	4.55 (22)	14.29 (28)	0.368
Clinical cure	83.43 (181)	67.69 (130)	0.010*
Microbiological cure	65.12 (43)	75.68 (37)	0.304

*P<0.05

of antimicrobial use in the study ward was 8 days, which was significantly lower than the control ward (10 days; P=0.031). These results are summarized in Table 3.

3.3. Clinical outcomes

The analysis revealed no significant differences in terms of infection-related mortality and microbiological cure between the study group and the control group. However, a higher rate of clinical cure was observed in the study group (83.43% vs. 67.69%, P=0.01). These results are presented in Table 4.

4. DISCUSSION

The aim of this prospective cohort comparative study was to investigate the impact of Antimicrobial Stewardship Programs (ASP) on the appropriate use of antimicrobial agents in a university hospital. Our findings revealed that the rate of appropriateness of antimicrobial use in the ASP unit was comparable to the control unit (67.96% vs. 68.46%, respectively; P=0.925). One notable result in our cohort was the substantial proportion of inappropriate antimicrobial use stemming from prescriptions lacking clear indications, as identified through the drug use evaluation forms.

These results align with previous studies conducted in university hospitals and tertiary care hospitals in Thailand. For instance, Aswapokee et al.[10] conducted a study on antimicrobial utilization patterns in medical wards of a university hospital in Bangkok, which revealed an incidence of appropriate use at 9%, largely due to the lack of evidence supporting the presence of infection. However, their study also reported a similar incidence of appropriate use for empirical treatment, approximately 64.16%, which is consistent with our findings. Udomthavornsuk et al.[11] conducted a prospective survey of antimicrobial use in a university hospital in Khon Kaen, where they observed an appropriateness rate for empirical treatment of 57.7%, indicating a significant proportion of inappropriate use at 42.3% primarily attributed to the absence of clear indications. Similarly, Apisarnthanarak et al.[12] conducted a study in a tertiary care center in Thailand and reported an incidence of appropriate antimicrobial use of 75.2%. The main reason for inappropriateness identified in their study was the use of antimicrobial agents without sufficient evidence of infection. Lastly, Pungjitprapai et al.[13] conducted a study in a tertiary care hospital in Bangkok, Thailand, reporting a prevalence of appropriate antimicrobial use of 74.6%, with the lack of indications according to hospital antimicrobial use guidelines being the primary reason for inappropriateness. These consistent findings emphasized the ongoing need for interventions aimed at improving the appropriateness of antimicrobial use and addressing challenges related to prescribing practices, particularly the lack of clear indications. Integration of new technologies, such as rapid diagnostic tests, biomarkers, and decision support tools, in conjunction with ASP interventions, has the potential to enhance clinicians' decision-making abilities. These can aid in improving appropriateness of antimicrobial use[14-15].

One plausible explanation for the comparable rate of appropriate antimicrobial use between the study unit and the control unit, despite the implementation of the ASP in the study unit, is the presence of rotating residents in a teaching hospital who were assigned to both the study and control wards. It was possible that these residents brought the knowledge and prescribing practices acquired in the study ward to the control ward, leading to a decrease in inappropriate antimicrobial prescribing and an improvement in appropriate prescribing in the control unit. Furthermore, it is important to consider that antimicrobial use in a university hospital tends to be more appropriate compared to other settings due to the availability of infectious diseases consultations. Studies conducted by Apisarnthanarak A et al.[12] and Pungjitprapai A et al.[13] also performed multivariate analysis and found that one of the key factors influencing appropriate antimicrobial use is the involvement of infectious diseases specialists in the decision-making process. Additionally, our study was conducted in the department of internal medicine, where there is already a tendency to use antimicrobial agents judiciously compared to other departments. This could explain why there was no significant difference in the rate of appropriateness between the study and control wards. Consistent with the findings from a study by Pungjitprapai et al.[13] reported that admission to the medicine department was associated with a higher rate of appropriate antimicrobial use.

Although there was no significant difference in the rate of appropriateness of antimicrobial use between the study ward and the control ward, our findings revealed important benefits of the ASP implemented in the study ward. Specifically, we observed a higher rate of de-escalation in the ASP group compared to the control group (43.09% vs. 23.85%, P<0.01) and a shorter duration of antimicrobial use in the study ward compared to the control ward (8 vs. 10 days; P=0.031). This aligns with a study conducted by Avdic E, et al.[16], which evaluated the impact of antimicrobial stewardship interventions on reducing the duration of therapy for community-acquired pneumonia, the interventions consisted of educational initiatives and providing feedback to healthcare teams regarding antimicrobial agent's selection and duration. The results of the ASP showed a decrease in the median duration of antimicrobial therapy from 10 days to 7 days (P<0.001). Additionally, there was an increase in the frequency of narrowing or modification of antimicrobials based on susceptibility results during the intervention period compared to the control period (67% vs 19%). Similarly, a study by Fukuda T et al.[17] examined the effects of pharmacist-led antimicrobial stewardship programs on the duration of treatment for uncomplicated gram-negative bacteremia in patients admitted to a community hospital in Japan. The results revealed that the de-escalation rates were higher in the pharmacist-led ASP group compared to the control group, with rates of 32.4% and 12.5% respectively (*P*=0.08). Additionally, the number of days of antimicrobial treatment was significantly reduced in the pharmacist-led ASP group, with a median duration of 8 days compared to 14 days in the control group (*P*<0.001). Furthermore, a multicenter study conducted by Foolad F, et al.[18], assessed the impact of a prospective stewardship intervention on the duration of antimicrobial therapy for community-acquired pneumonia in the US. The study demonstrated that following the implementation of the ASP, the median duration of therapy decreased from 9 days to 6 days (*P*<0.001).

In additional analysis, our results demonstrated that there were no significant differences in terms of microbiological cure and infection-related mortality between the study group and the control group. However, a higher rate of clinical cure was observed in the study group. These results are consistent with the findings of a meta-analysis conducted by Davey et al.[19] in 2013 examined the impact of interventions aimed at improving antimicrobial prescribing practices for hospital inpatients. The findings of the meta-analysis demonstrated that interventions targeting excessive antimicrobial prescribing in hospitals can lead to a reduction in antimicrobial resistance and hospital-acquired infections. Additionally, interventions focused on improving the effectiveness of prescribing can result in improved clinical outcomes, such as increased infection cure rates and decreased treatment failures, while also helping to minimize adverse drug reactions and *Clostridium difficile* infections. Moreover, in an updated systematic review by Davey et al.[20] in 2017, the results reaffirmed the effectiveness of interventions in increasing compliance with antimicrobial use policies and reducing the duration of antimicrobial treatment. They also found that lower use of antimicrobial agents probably does not increase mortality.

The lack of differences in infection-related mortality between the two groups may be attributed to the small number of patients in our study who had documented infection-related deaths in their medical records. Only one patient in the study ward and four patients in the control wards were recorded as having died due to infection. Additionally, the absence of significant differences in microbiological cure in our cohort can be attributed to the fact that not all patients underwent repeated microbiological sampling to confirm their microbiological response. It is worth noting that in certain diseases such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), microbiological cure does not always correlate with clinical cure[21]. However, despite the lack of significant differences in infection-related mortality and microbiological cure, it is important to highlight that the implementation of the ASP did not compromise clinical outcomes. This indicates that the ASP was effective in promoting optimal antimicrobial use without negatively affecting clinical outcomes.

There are some important limitations to consider in our study. Firstly, our study focused on appropriate empirical treatment, which often involves the initial administration of broad-spectrum antimicrobial agents to cover a wide range of potentially resistant pathogens in severely ill patients. However, our interventions in the study unit did not include strategies such as preauthorization, which could have further optimized initial empiric therapy[22]. Additionally, the absence of rapid diagnostic tests or novel biomarkers to aid in appropriate empirical treatment limited our ability to enhance the optimization of antimicrobial therapy[23]. This inherent approach to empirical treatment may have contributed to the lower rate of appropriateness observed in our study, as the initial choice of antimicrobial agents may not always align perfectly with the criteria outlined in the drug use evaluation forms. Secondly, it should be noted that the availability of a pharmacist in the study ward was limited to operating hours, which restricted their ability to provide continuous oversight and intervention in antimicrobial prescribing outside of these hours. This limitation could have impacted the timely adjustment of antimicrobial therapy and the implementation of ASP recommendations during non-operating hours. Lastly, our study did not include a multivariate analysis to identify specific factors that could have influenced the primary outcome. Conducting multivariate analysis to explore the potential factors influencing appropriateness of antimicrobial use would require further research and larger studies.

5. CONCLUSION

The implementation of ASP demonstrated positive effects on the de-escalation rate and treatment duration. While the overall appropriateness of antimicrobial treatment in the study ward did not significantly increase, the ASP did not compromise clinical outcomes. Further research and interventions are warranted to enhance the appropriate use of antimicrobial agents and mitigate the potential risks associated with inappropriate prescribing practices in hospital settings.

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Conflict of interest
None to declare.

Funding
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Ethics approval
This study obtained approval from the research ethics review committee for research involving human research participants at the Faculty of Medicine, Chulalongkorn University (COA No.349/2015-IRB No.076/58) and the ethics committee of Faculty of Dentistry/Faculty of Pharmacy, Mahidol University (COA.No.MUDT/PY-IRB 2015/025.2206).

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