Evaluation of Clinical and Cost Outcomes of the Antimicrobial Stewardship Programme in a Tertiary Referral Hospital in Perak, Malaysia

Cheah Meng Fei[1], Thong Kah Shuen[1], Cheng Joo Thye[2], Ker Hong Bee[2]

[1] Department of Pharmacy, Hospital Raja Permaisuri Bainun, Perak, Ministry of Health Malaysia
[2] Department of General Medicine, Hospital Raja Permaisuri Bainun, Perak, Ministry of Health Malaysia

Abstract

Introduction: The antimicrobial stewardship (AMS) programme has been implemented in most public healthcare facilities in Malaysia to promote judicious use of antimicrobials and to minimise antimicrobial resistance. Routine AMS ward rounds are one of the activities in the AMS programme.

Objective: This study aimed to evaluate the clinical outcomes of patients managed under the AMS programme in a Malaysian tertiary hospital, with the antimicrobial cost savings consequential to the recommendations provided by the AMS team during the routine AMS ward rounds.

Methods: This is a retrospective review of the AMS database in Hospital Raja Permaisuri Bainun, Perak from 1 January 2019 to 30 June 2019. The AMS clerking forms filled during ward rounds were reviewed and relevant data were collected. Cases with incomplete information or recommendations that had no direct impact on patients' clinical and cost outcomes were excluded.

Results: A total of 200 cases were referred to the AMS team for recommendations. Of those recommendations, 167 (83.5%) were accepted by the primary team. Most of the cases (76.0%) were discharged well. There was no association between duration of antimicrobial therapy ($p=0.147$), length of stay ($p=0.849$), 30-day infection-related mortality ($p>0.95$) and 30-day infection-related readmission ($p=0.329$) with acceptance of those recommendations. Accepting the recommendations contributed to a total antimicrobial cost saving of RM9,579.82 but rejection resulted in cost wastage of RM1,332.18 over the study period ($p<0.001$).

Conclusion: Recommendations provided by the AMS team resulted in cost savings without compromising other clinical outcomes. Future studies should evaluate the potential long-term benefits of AMS programme and the sustainability of these benefits.

Keywords: antimicrobial stewardship programme, AMS ward rounds, clinical outcomes, antimicrobial cost savings, Malaysian tertiary hospital

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Corresponding Author: Cheah Meng Fei,
Department of Pharmacy, Hospital Raja Permaisuri Bainun, Jalan Raja Ashman Shah, 30450 Ipoh, Perak.
E-mail: mfcheah85@hotmail.com

Introduction

The development of antimicrobial agents provided a temporary solution in struggling pathogenic microorganisms (1). However, the inappropriate use of antimicrobial agents has been associated with antimicrobial resistance. Antimicrobial resistance is currently a serious threat to human health globally that requires urgent attentions and interventions (2). The most commonly reported resistant bacteria in Malaysia were *Staphylococcus aureus*, *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (3).

The antimicrobial management or stewardship programme has been developed as a response to antimicrobial resistance. Antimicrobial stewardship (AMS) has been defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration" (4). The AMS programme consists of various strategies such as education, formulary restriction, preauthorisation, prospective audit and feedback (1,4). Often, different strategies are combined in the AMS bundles. The objectives of the AMS programme are to improve patient outcomes, to optimise antimicrobial therapy, to limit any unintended consequences and to reduce healthcare costs without adversely impacting the quality of care (5). One of the AMS core activities is to formalise regular antimicrobial rounds by the

AMS team in hospitals (5). The AMS team of Hospital Raja Permaisuri Bainun (HRPB) in Ipoh, Perak, consisting of infectious diseases physicians, clinical pharmacists and clinical microbiologists, was established in October 2013.

It should be noted that the primary goal of any AMS programmes is not to reduce antimicrobial consumption, but instead is to improve the quality of patient care and subsequently to optimise antimicrobial costs. Several systematic reviews showed that AMS interventions increased compliance with local antimicrobial policies and improved patient outcomes (6,7). The Malaysian AMS protocol has also stated several process and outcome measures to evaluate the effectiveness of the AMS programme activities (5). Hence, in line with the placement of a dedicated pharmacist in the AMS team commencing January 2019 in HRPB, this study was performed to evaluate the impact of recommendations made by the AMS team during antimicrobial rounds on patients' clinical outcomes and antimicrobial cost savings.

Methods

Study Design and Setting

This study was conducted via retrospective review of the AMS database in HRPB. The AMS case clerking forms of all patients were reviewed and relevant data for each patient was collected. Cases reviewed by the AMS team between 1 January 2019 to 30 June 2019 involving patients with age 13 years old and above were included in this study. The cases were excluded if the AMS team provided recommendations that had no direct impact on patients' clinical and cost outcomes, such as to continue on existing antimicrobial regimen and any non-antimicrobial agent-related recommendations such as requirement of additional investigations, infection control measures or referral of complicated cases to the infectious diseases team.

Description of the AMS Programme

One of the activities implemented by the team was to conduct regular AMS ward rounds and this normally starts with case identification. Besides receiving case referral from the ward pharmacists, medication charts in the satellite pharmacies are reviewed by one of the AMS pharmacists on a daily basis. The details of all patients prescribed with carbapenems and vancomycin as well as cases with suspected inappropriate use of antibiotics were recorded in a screening list. Subsequently, cases in the screening list were reviewed in the ward. Cases with confirmed inappropriate use of antibiotics requiring infectious diseases physician assessment were referred to the AMS team. The use of antibiotics was considered to be inappropriate if one or more of the following criteria were met:

i. the hospital antibiotic guidelines (8) were not adhered without valid reasons
ii. the dosage, duration of therapy and/or empirical treatment choice was/were inappropriate according to the available guidelines
iii. a narrower- or broader-spectrum agent should be used based on the culture and sensitivity results
iv. infections did not present (i.e. due to bacteria colonization or an alternative explanation for the clinical presentation)

During the rounds, comprehensive discussions were performed on the identified cases. Following the discussion, the recommendations made by the AMS team were documented on an AMS sticker and it was then pasted on the patient's medical record. A direct feedback was also provided verbally to the primary team. The MAS team may provide one or more of the following recommendations:

i. continuation of the same regimen
ii. discontinuation of the antimicrobial agents
iii. de-escalating existing regimen based on culture and sensitivity results
iv. escalating existing regimen based on culture and sensitivity results
v. conversion of antimicrobial agents from parenteral route to oral route
vi. dose optimisation of the antimicrobial agents
vii. others (e.g. infection control measures, refer experts, re-investigate cultures etc.)

All cases were followed up for 30 days from the first day of the recommendation was made to determine the outcomes. The details of the cases were documented in an AMS clerking form.

Data Collection and Outcomes

The required information was collected from the AMS clerking forms and recorded in a data collection form. Data extracted included clinical characteristics, the reason of referral to the AMS team for review, recommendations made by the AMS team, the acceptance of the recommendations, clinical outcomes, and the change in antimicrobial cost.

The clinical characteristics included types of infection, antibiotics used and the prescribers. The reason of the cases to be referred to the AMS team for review was classified into the following categories:

i. inappropriate choice of antibiotics based on hospital antibiotic guidelines
ii. inappropriate duration of therapy
iii. inappropriate combination of antibiotics
iv. inappropriate antibiotic chosen for definitive therapy
v. others (e.g. infection was not present, inappropriate dosing regimen etc.)

For the purpose of this study, only recommendations made by the AMS team during ward rounds that had direct impact on patients' clinical and cost outcomes were evaluated. Those recommendations included:

i. discontinuation of the antibiotic regimen
ii. de-escalation of the existing antibiotic regimen
iii. escalation of the existing antibiotic regimen
iv. conversion of the antibiotic regimen from parenteral route to oral route
v. dose optimisation of the antibiotic regimen

The acceptance or rejection of the recommendations made by the AMS team during ward rounds was determined by reviewing the case in the ward within 24 hours after the recommendation was made. If the recommendations were accepted after this timeframe, they were still considered to be rejected for the purpose of this study.

The clinical outcomes evaluated were the duration of therapy with antimicrobial agents, the length of stay (LOS), the absence or presence of 30-day inpatient mortality and 30-day readmission. The duration of therapy was defined as the number of days the antibiotics were given in the ward. The LOS was defined as the number of days from the first day of admission to the day of discharge. The 30-day inpatient mortality was defined as patients who died, during hospitalisation, within 30 days from the first day of the recommendations made by the AMS team. If the cause of death was due to infection, then such death was defined as infection-related mortality. The 30-day infection-related readmission was defined as readmission due to infection that occurred within 30 days of the date of discharge. The clinical outcomes, especially the cause of death and cause of readmission, were obtained from the discharge summary of the patient.

The cost outcome for each case was evaluated in terms of the changes in antimicrobial cost. The change in antimicrobial cost was defined as the estimated difference between the cost incurred from the original prescription of the antimicrobial agents prior to the AMS recommendation and the cost after adopting the AMS recommendation (5). It was expressed in terms of Ringgit Malaysia (RM). The cost of an antimicrobial agent was calculated in terms of the number of ampoules / vials / tablets / capsules supplied multiplied by the government-approved unit price of that particular agent. The government-approved unit price was obtained from Pharmacy Information System (PhIS), Ministry of Health Malaysia, and the information was accessed on 1st November 2019. Figure 1 showed the calculation of the changes in antimicrobial costs.

Data Management and Statistical Analysis

The clinical characteristics of the cases, the reasons of referral to the AMS team for review, recommendations made by the AMS team, the acceptance of the recommendations, clinical outcomes and the change in antimicrobial cost were descriptively reported either in percentages or median (interquartile range, IQR). The Mann-Whitney test was used to compare the difference in the duration of antibiotic therapy, length of stay (LOS) and the change in antimicrobial cost between the recommendation acceptance and rejection groups. The Fisher's exact test was used to compare the difference in mortality and readmission between the recommendation acceptance and rejection groups. The significance level was set at $p<0.05$.

Ethics of the Study

Institutional approval to conduct this study was obtained from the head of department and hospital director before data collection. This study was also approved by Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia [KKM/NIHSEC/P19-2303(5)] (NMRR-19-2761-50838). All data obtained from the AMS database was kept confidential.

Calculation of Antimicrobial Cost

If an antimicrobial agent was discontinued

The change in cost = cost of the agent × cost saving days

If an antimicrobial agent was switched

The change in cost = (cost of the previous agent × cost saving days) – (cost of the new agent × cost saving days)

Cost saving days

- The number of days to the intended completion date of the antimicrobial agent.
- If the intended date of completion was not known, then the no. of days to the nearest multiple of 7 (e.g. 7 days, 14 days, 21 days etc.) was chosen based on the type of infection.

Note:

i. *A value with a positive sign indicated cost saving and that with a negative sign indicated cost wastage.*
ii. *The sign of the value obtained was reversed if the recommendations provided by the AMS team were not accepted.*

Figure 1: Calculation of the changes in antimicrobial cost with and without acceptance of the AMS team's recommendations

Results

Between January and June 2019, a total of 239 cases were reviewed by the AMS team. After excluding cases based on the exclusion criteria (33 continuation of existing antimicrobial regimen and 6 incomplete data), a total of 200 cases were included into the study. The total number of patients involved were 190 patients. Of those patients, 182 were reviewed once, 6 were reviewed twice and 2 were reviewed thrice, respectively, by the AMS team. Table 1 showed the five most encountered infections and reviewed antibiotics. Of the 200 cases, 150 (75.0%) were prescribed with one antibiotic, 45 (22.5%) were prescribed with two antibiotics and 5 (2.5%) were prescribed with three antibiotics. Almost one-half (49.5%) of the cases were reviewed from the Department of General Medicine followed by the Department of General Surgery (17.5%).

Table 2 showed the reasons of referral to the AMS team for review. Either one or two recommendations were made by the AMS team for each case referred. The number and types of the first recommendation made by the AMS team were summarised in Table 2. Fifteen cases (7.5%) had a second recommendation made. However, those recommendations were non-antibiotic-related such as recommendations to perform additional investigations, infection control measures or referral of complicated cases to the infectious diseases team. The overall acceptance of the recommendations made by the AMS team within 24 hours was 83.5% (167/200).

The cases in the study were followed up for 30 days from the first day of the recommendation made by the AMS team to determine their clinical outcomes. Of the 200 cases reviewed by the AMS team, 152 (76.0%) were discharged well, 10 (5.0%) were still hospitalized, 20 (10.0%) were transferred out to other healthcare facilities and 18 (9.0%) passed away. Of the 152 cases that were discharged well, 18 (11.8%) were re-admitted due to infection within 30 days of discharge. Of the 18 cases that died, 15 (83.3%) were due to infection.

Table 3 showed the comparison of clinical outcomes and antimicrobial cost savings between acceptance and rejection of AMS recommendations. Accepting the AMS recommendations did not affect the clinical outcomes in terms of the median duration of antibiotic therapy ($p=0.147$), length of stay ($p=0.849$), 30-day infection-related mortality rates ($p>0.95$) and 30-day infection-related readmission rates ($p=0.329$). However, it saved a total of RM9,579.82 (RM57.36 per case). Conversely, an extra cost of RM1,332.18 (RM40.37 per case) was spent as a result of rejecting the AMS recommendations ($p<0.001$).

Table 1: General characteristics of the reviewed cases (n=200)

Characteristic	n (%)
Five most encountered infections	
Community-acquired pneumonia	28 (14.0)
Hospital-acquired pneumonia	25 (12.5)
Surgical / traumatic wound infections	11 (5.5)
Urosepsis	10 (5.0)
Infective diarrhoea	8 (4.0)
Five most reviewed antibiotics	
Meropenem	44 (22.0)
Ceftriaxone	43 (21.5)
Piperacillin / tazobactam	14 (7.0)
Ceftazidime	14 (7.0)
Amoxicillin / clavulanic acid	13 (6.5)

Table 2: The reasons of referral to the AMS team and types of recommendation made (n=200)

Characteristic	n (%)
Reason	
Inappropriate choice of antibiotics based on hospital antibiotic guidelines	116 (58.0)
Inappropriate duration of therapy	21 (10.5)
Inappropriate combination of antibiotics	12 (6.0)
Inappropriate antibiotic chosen for definitive therapy	11 (5.5)
Others (infection was not present, inappropriate dosing regimen etc.)	40 (20.0)
Recommendation	
Discontinuation of the antibiotic regimen	83 (41.5)
De-escalation of the existing antibiotic regimen	91 (45.5)
Escalation of the existing antibiotic regimen	14 (7.0)
Conversion of the antibiotic regimen from parenteral route to oral route	9 (4.5)
Dose optimization of the antibiotic regimen	3 (1.5)

Table 3: Comparison of outcomes between the cases with acceptance and rejection of AMS recommendations

Variable	Recommendations accepted	Recommendations rejected	p-value
Mortality, n (%)			0.750 [a]
Yes	14 (10.1)	4 (12.5)	
No	124 (89.9)	28 (87.5)	
Infection-related mortality, n (%)			> 0.95 [b]
Yes	12 (85.7)	3 (75.0)	
No	2 (14.3)	1 (25.0)	
Infection-related readmission, n (%)			0.329 [c]
Yes	13 (10.5)	5 (17.9)	
No	111 (89.5)	23 (82.1)	
Duration of therapy (days), median (IQR)	11.00 (6.00, 16.75)	13.50 (7.25, 22.00)	0.147 [d]
Length of stay (days), median (IQR)	10.00 (6.00, 19.00)	9.50 (3.25, 25.75)	0.849 [d]
Cost savings (RM), median (IQR)	45.45 (14.37, 100.80)	-9.06 (-91.60, 11.16)	< 0.001 [e]

[a] Fisher's exact test, n=170; [b] Fisher's exact test, n=18; [c] Fisher's exact test, n=152; [d] Mann-Whitney test, n=152; [e] Mann-Whitney test, n=200

Discussion

Cases referred to the AMS team for ward rounds were mostly complicated and required infectious diseases physician assessment. Such cases were mainly referred due to inappropriate choice of antibiotics and duration of therapy or antibiotics not indicated. Hence, the types of recommendation made by the AMS team were mostly either discontinuation or de-escalation of the existing antibiotic regimen. Although prescribing

antibiotics for a longer duration than necessary or that were of broader spectrum than necessary could effectively treat the infections, such practices may result in the detrimental effects on ecological pressure and the emergence of antimicrobial resistance (2). Nevertheless, the AMS team occasionally recommended escalation of the existing antibiotic regimen based on patients' clinical presentation and the latest culture and sensitivity reports. Only 1.5% of the recommendations were dose optimisation of the antibiotic regimen. Such findings showed that the prescribers were generally aware of the dosing regimen of antibiotics in view of the availability of various materials of references. In the wards with ward pharmacists, they would have intervened prescriptions with inappropriate doses of antibiotics so that these cases need not be referred to the AMS team.

The overall acceptance of the recommendations made by the AMS team within 24 hours was 83.5%. A similar study conducted by Liew *et al*. in Singapore General Hospital showed that the acceptance of the recommendations by the primary management team was 77.8% (9). The recommendations made during AMS ward rounds, which were classified as a prospective audit and feedback strategy, were generally associated with a higher overall acceptance rate and less vulnerable to active rejection because the primary management team did not perceive the loss of autonomy in clinical decision and prescribing (10). The acceptance of recommendations was also voluntary rather than mandatory compared to other AMS strategies such as formulary restrictions and preauthorisation. This strategy had also provided opportunities for education and learning through case discussions and the feedback mechanism (10). This strategy also ensured individualisation of therapy, allowing patients' clinical characteristics and concomitant drugs to be considered (10).

There were no significant differences in the clinical outcomes, namely the median duration of antibiotic therapy, length of stay, 30-day mortality rates and 30-day infection-related readmission rates, between the recommendations acceptance and rejection groups in this study. In fact, such findings were heterogeneous among different studies conducted in different countries such as Africa, Hong Kong, Singapore, Spain and the United States (9,11-16) where some studies showed improvement in clinical outcomes among patients after accepting AMS interventions or recommendations while some studies showed no significant difference. However, direct comparison of the findings could not be made due to different study designs and different combination of AMS strategies used in these studies. Furthermore, the clinical outcomes of patients might be affected by many potential confounding factors such as the case mix of the patients, and it is therefore difficult to relate the impact of acceptance of AMS recommendations to the clinical outcomes.

The acceptance of AMS recommendations team was generally associated with significant antimicrobial cost savings in this study. Our findings were similar to those demonstrated in the studies conducted in Abu Dhabi, Hong Kong, Singapore, South Africa and Taiwan (13,15-18). AMS recommendations such as the discontinuation of existing antibiotic regimen reduced the duration of antibiotic therapy and therefore reduced the antimicrobial cost. De-escalation from a broad-spectrum antibiotic regimen to a relatively less costly narrow-spectrum antibiotic regimen also helped to reduce the antimicrobial cost.

The main objectives of the AMS activities are to ensure judicious use of antimicrobial agents and to minimise antimicrobial resistance. Some prescribers, however, were worried that accepting the AMS recommendations could adversely affect the clinical outcomes of their patients as they need to limit the use of broad-spectrum antimicrobial agents and reduce the duration of treatment (15). Some of them also believe that the AMS programme emphasises on the restriction of antimicrobial consumption and cost savings rather than improving the quality of patient care (15). Such an impression was not supported by the results of this study because accepting the AMS recommendations was not associated with unpredicted adverse clinical outcomes. Conversely, it was demonstrated that through rational selection and prescription of antibiotics, inappropriate consumption and expenditure could be reduced.

There are several limitations in this study. The retrospective nature of the study caused inadequate data to be collected. For example, we did not record the baseline demographic and clinical characteristics of the patients, which disallowed us to accurately assess the differences in the patient populations during data analysis. Secondly, we only assessed the clinical outcomes for inpatients within the same hospital. Hence, some of the important clinical outcomes, such as mortality in other facilities for patients who were transferred out from this hospital and readmissions to other healthcare facilities, were not captured. Thirdly, the government-approved unit price and the brand of the antibiotic might change with time and our data analysis was based on the unit price and brand on 1st November 2019. Therefore, the any changes in the unit prices and brands of antibiotics throughout the 6-month study period might cause discrepancy in terms

of cost savings estimation. Furthermore, the differences in purchasing agreements between institutions and variability in antimicrobial costs from country to country also did not allow any generalisation of our findings. Lastly, this study only assessed the impact of one type of AMS activity, namely the AMS ward rounds. A successful AMS bundle usually incorporates more than one activity or strategies. Hence, future studies should focus on the impact of different AMS strategies and to include other important outcomes such as improvement in appropriateness of antimicrobial prescriptions, infection-related hospitalisation rates, the prevalence of antimicrobial-related side effects and the impact of the AMS programme on antimicrobial susceptibility pattern.

Conclusion

The study demonstrated that the acceptance rate of recommendations provided by the AMS team during ward rounds was high. The acceptance of the recommendations had resulted in cost savings without compromising patients' clinical outcomes. This study highlighted the need of continuous efforts by the AMS team to ensure the sustainability of those outcomes in order to improve the quality of care of patients, to reduce healthcare costs and to minimise antimicrobial resistance.

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Conflict of interest statement:

All the authors have nothing to disclose regarding financial or personal relationships that may have a direct or indirect interest in the subject matter of this publication.

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