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Original Research

Impact of printed antimicrobial stewardship recommendations on early intravenous to oral antibiotics switch practice in district hospitals

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Abstract

Background: Early intravenous to oral (IV-PO) antibiotics switch, which is one of the important elements in antimicrobial stewardship (AMS) is not well implemented in Malaysian district hospitals. A systematic interventional strategy is required to facilitate IV-PO antibiotic switch.

Objective: This study aimed to evaluate the impact of printed AMS recommendations on early IV-PO antibiotics switch practice in district hospitals.

Methods: This study was an interventional study conducted in medical wards of eight Sarawak district hospitals from May to August 2015. In pre-intervention phase, pharmacists performed the conventional practice of reviewing medication charts and verbally informed the prescribers on eligible IV-PO switches. In post-intervention phase, pharmacists attached printed checklist which contained IV-PO switch criteria to patients' medical notes on the day patients were eligible for the switch. Stickers of IV-PO switch were applied to the antibiotic prescription to serve as reminders.

Results: 79 and 77 courses of antibiotics were studied in the pre-intervention phase and post-intervention phase respectively. Timeliness of switch was improved by 1.63 days in the post-intervention phase (95%CI 1.26:2.00 days, $p<0.001$). Mean duration of IV antibiotics in the post-intervention phase was shorter than pre-intervention phase (2.81 days (SD=1.77) vs 4.05 days (SD=2.81), $p<0.001$). The proportion of IV-PO switches that were only performed upon discharge reduced significantly in the post-intervention phase (31.2% vs 82.3%, $p<0.001$). Length of hospital stay in the post-intervention phase was shortened by 1.44 days ($p<0.001$). Median antibiotic cost savings increased significantly in the post-intervention phase compared to the pre-intervention phase [MYR21.96 (IQR=23.23) vs MYR13.10 (IQR=53.76); $p=0.025$].

Conclusions: Pharmacist initiated printed AMS recommendations are successful in improving the timeliness of IV-PO switch, reducing the duration of IV, reducing the length of hospitalisation, and increasing antibiotic cost savings.

Keywords

Anti-Bacterial Agents; Antimicrobial Stewardship; Drug Administration Routes; Pharmacy Service, Hospital; Pharmacists; Evaluation Studies as Topic; Malaysia

INTRODUCTION

Antibiotics have been prescribed in an uncontrolled and injudicious trend which leads to an increase in healthcare costs and antibiotic resistance.¹ As a response to this emerging crisis, antimicrobial stewardship (AMS) protocol have been introduced by Ministry of Health Malaysia in 2015 for streamlining the use of antibiotics, one of the strategies being intravenous (IV) to oral (PO) antibiotic switch.² A study carried out by Sevinc *et al.* in a large teaching hospital in the United States concluded that 40% of patients starting on IV antibiotics were eligible for an early IV-PO switch, in which short intravenous therapy were given for 2-3 days, followed by oral treatment for the remainder of the course.³ Similar result was shown by a prospective observational study carried out in hospitalized patients with community-acquired pneumonia.⁴ However, the practice of early switch to oral antibiotics has not been implemented fully in hospital clinical setting, in which most of the studies showed that 60-75% of eligible patients did not receive the IV-PO switch.⁵⁻⁷

Early switch of IV antibiotics resulted in equal clinical efficacy compared with patient administered with full parenteral course.⁸⁻¹¹ Advantages of an early iv- oral switch include decreased risk of infection of the iv catheter, decreased risk of thrombophlebitis, increased comfort and mobility for the patient, and the possibility of earlier discharge from the hospital.⁸ Furthermore, oral therapy is less labour intensive for the nursing staff, and economic benefits are clear due to hidden costs of IV administration, such as cost of diluents, equipment for administration, needles, syringes, and nursing time.^{7,12}

The Infectious Diseases Society of America (IDSA) recommends institutions to introduce a systematic plan for switching from IV to PO antimicrobial therapy, facilitated by the development of clinical criteria and guidelines for switching to oral agents.¹³ A study carried out in a community hospital in Canada reported that implementation of clinical intervention form had reduced IV antibiotic duration by 42%.¹⁴ A checklist with criteria for switching to oral antibiotics in general medical wards was shown to shorten the duration of IV antibiotics without any negative effect on treatment outcome.¹⁵ In the United Kingdom, IV-PO switch promotion is implemented through IV-PO antibiotic switch protocol in wards, pharmacy intervention forms, and reminder notes in medication

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charts.¹⁶⁻¹⁸ Timeliness of switch, length of stay and antimicrobial cost savings were improved through the application of stickers and criteria for the switch to the drug charts than conventional practice of giving verbal reminders.¹⁹

Many doctors were not aware of the existence of any clear guidelines on the adequate timing of the switch.²⁰ Furthermore, an interview conducted by a group of researchers discovered that one of the barriers of IV-PO switch was doctors' unawareness of which patients were on intravenous antibiotics and those to whom the guideline applies. One of the solution to overcome this barrier was the reminder stickers that were affixed to the medication charts.²¹ In Malaysia, a cross-sectional study conducted to explore clinicians' baseline knowledge, practice beliefs and acceptance of IV-PO switch practice in a tertiary hospital had found that 47% of clinicians agreed that 'patient should receive a standard duration of IV antibiotic'.²² In district hospitals in Sarawak, although ward pharmacists are present in the wards to conduct routine review on patients' prescriptions and giving verbal recommendations when necessary, there are no systematic interventional strategies to facilitate the IV-PO antibiotics switch.

We conducted a before and after interventional study to compare the conventional practice by giving verbal reminders to doctors on IV-PO switch with implementing printed AMS recommendations. This study aimed to evaluate the impact of printed AMS recommendations on early IV-PO antibiotics switch practice in district hospitals, with regards to the comparison of timeliness of IV-PO switch, duration of IV antibiotics, mean length of hospital stay, and antibiotics cost savings pre and post implementation of printed AMS recommendations.

METHODS

This study was a cross-sectional interventional study conducted prospectively in eight Sarawak district hospitals from May to August 2015, namely Hospital Bau, Hospital Lundu, Hospital Betong, Hospital Saratok, Hospital Mukah, Hospital Dalat, Hospital Limbang and Hospital Lawas with total beds number of 474 as shown in Table 1. This study was divided into 2 phases, which was pre-intervention and post-intervention. Pre-intervention phase was conducted from May to June 2015, while post-intervention was conducted from July to August 2015. The study was performed in accordance with the ethical principles in the Declaration of Helsinki and that are consistent with Good Clinical Practice. Approval has been obtained from the Medical Research and Ethics Committee to conduct this study.

Table 1. Beds number and total number of pharmacists of each hospital involved		
Hospital	Beds (n)	Pharmacists (n)
Hospital Mukah	80	4
Hospital Dalat	8	2
Hospital Saratok	78	6
Hospital Limbang	100	6
Hospital Lawas	46	2
Hospital Betong	48	4
Hospital Bau	68	4
Hospital Lundu	46	4
Total	474	32

Subjects

Patients eligible for IV-PO switch fulfilled these criteria: 18 years and above, received an IV antibiotic for more than 48 hours, body temperature $<38^{\circ}\text{C}$ for the past 24 hours, normal or decreasing white cell count, tolerating orally and showing clinical improvements from signs of infection. In this study, one of the switch criteria is patient must be at least on IV antibiotics for at least 48 hours, which lessen the risk and possibilities that the intravenous to oral switch may be occurring too early, resulting inadequate treatment of the infection.³ 'Clinical improvement' for community-acquired pneumonia comprises of resolution of tachypnea and pulse rate $<100\text{ beats/min}^{23}$; for cellulitis it includes reduced swelling, redness, pain and warmth.

Excluded from the study were patients younger than 18 years of age, oral route compromised (vomiting, nil by mouth, severe diarrhoea, swallowing disorder, unconscious, active gastrointestinal bleeding, malfunctioned gastrointestinal tract or malabsorption syndrome), continuing sepsis (2 or more of the following: Temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate $>90\text{bpm}$, respiratory rate $>20/\text{min}$, white cell count >12 or <4), deteriorating clinical condition, prolonged course of IV antibiotics needed (eg: endocarditis, meningitis, *Staphylococcus aureus* bacteraemia, immunosuppression, bone and joint infection, deep abscess, empyema, cystic fibrosis, orbital cellulitis, endophthalmitis, prosthetic infection and melioidosis), febrile with neutropenia, absence of oral formulation that fit the susceptibility, hypotension (systolic blood pressure $<90\text{ mmHg}$, diastolic blood pressure $<60\text{ mmHg}$), and shock.^{2,3,7,17}

Intervention

In this study, convenience sampling method was used as the data collection was fit into the work timetable of the ward pharmacists of each study hospitals. One ward pharmacist from each study hospitals was assigned as study investigators. The ward pharmacists identified cases eligible for inclusions through daily screening of the medication charts in the ward, except on weekends when ward pharmacy service was unavailable.

All the patients eligible for IV-PO switch were followed up prospectively by the study investigators. In pre-intervention phase, the investigators performed the conventional practice of reviewing antibiotic prescriptions in the wards and verbally informed the prescribers on the day patient was eligible for switching to oral antibiotics. In post-intervention, a clinical intervention form (online appendix) with the criteria of IV-PO switch and recommendation of a suitable oral antibiotic was attached to the medical notes on the day patients were eligible for the switch. Doctors were required to document on the form whether the switch recommendation was accepted and stated the reasons if the recommendations were being rejected. An IV-PO switch sticker was placed beside the antibiotic prescription in the medication charts to serve as a reminder for IV-PO switching. All the doctors in the study hospitals were handed a written formal letter by the research investigators of each study hospitals on the availability of IV-PO switch protocol in the wards one week before the post-intervention phase commenced. The IV-PO protocols

Characteristics	Pre intervention	Post intervention
Num. of patients	72	76
Female, n (%)	31 (39.2)	34 (44.2)
Num. IV antibiotic courses	79	77
Age (years): mean (SD)	57.18 (17.86)	58.52 (17.87)
Site of Infection: n (%)		
Respiratory Tract	44 (55.7%)	47 (61.0%)
Skin and Soft Tissue	12 (15.2%)	10 (13.0%)
Urinary Tract	14 (17.7%)	9 (11.7%)
Others	9 (11.4%)	11 (14.3%)

were also attached to the letters. The study investigators followed up the patients daily until IV-PO switch was done or until patients were discharged home (whichever was earlier). The conventional practice of clinical pharmacists reviewing drug charts and contacting prescribers to discuss a switch to an oral antimicrobial was continued throughout the post-intervention phase.

Outcome measures

In our study, the primary outcome measured was timeliness of IV-PO switch. 'Timeliness' was defined as differences in days between the actual switch and the days patients met criteria for a switch to oral therapy.

The secondary outcomes measured were duration of IV antibiotics, length of hospital stay, and antibiotic cost savings. 'Duration' was defined as total days of IV antibiotics given from the first dose until the last IV dose in the ward. 'Length of hospital stay' was defined as the total number of days patient stayed in hospital from the first day of admission until the day of discharge home. 'Antibiotics cost savings' was defined as cost savings incurred by switching IV antibiotic to oral antibiotic, as was calculated from the formula:

$$\text{Cost savings} = (\text{Cost of IV antibiotics} \times \text{cost-saving days}) - (\text{Cost of oral antibiotics} \times \text{cost savings days}).$$

Cost savings days was defined as number of days of oral antibiotics including the duration of discharged oral antibiotics.²

Data collection

A data collection form was developed, which required the investigators to record the following information obtained from the medication charts, medical notes and discharge prescriptions: Age and gender of switch eligible patients, diagnosis (as per determined by medical officer either clinically, microbiologically, or both), admission date, IV antibiotics started, time taken for switching, total duration of IV antibiotics in ward, oral antibiotics switched, duration of oral antibiotics, date of discharge, whether IV antibiotic was restarted for the same indication after IV-PO switch, and whether the switch was only done upon discharge. The data collection form was pretested through a pilot study in Hospital Mukah for one week to ensure suitability. All investigators were briefed regarding the data collection to ensure reliability.

Data Analysis

Based on the calculation done using Power and Sample Size Calculator (Dupont and Plummer, 1997), the minimum

	Pre intervention	Post intervention
IV ampicillin	8 (10.1)	15 (19.4)
IV amoxicillin-clavulanic acid	28 (35.4)	34 (44.2)
IV benzylpenicillin	4 (5.1)	1 (1.3)
IV ceftriaxone	7 (8.9)	1 (1.3)
IV cefuroxime	16 (20.3)	12 (15.6)
IV cloxacillin	7 (8.9)	5 (6.5)
IV metronidazole	2 (2.5)	4 (5.2)
IV ampicillin- sulbactam	5 (6.3)	5 (6.5)
IV azithromycin	2 (2.5)	
Total	79	77

sample size required was 128 patients (64 patients in each group) and at 80% certainty with a precision of 0.05 and estimated standard deviation of 2.

The data collected was transcribed into Excel spreadsheet. Statistical analysis was performed using the SPSS version 20.0. Descriptive statistics were used to describe percentage of IV courses switched to oral on appropriate day (day of criteria for switch met), percentage of IV-PO switched performed only upon discharge, percentage of patients requiring reinstatement of IV antibiotics after switch to oral as well as continuous variables such as timelines of switch, length of hospital stay, duration of IV antibiotics in ward, and antibiotics cost savings. The two groups of patients (pre and post intervention) were compared for mean timeliness of IV to oral switch, length of hospital stay, duration of IV antibiotics using independent t-test. Median antibiotic cost savings between two groups were compared using Mann-Whitney test. Fisher's Exact Test was used to compare the number of IV-PO switches performed on the appropriate day, number of IV-PO switches performed only upon discharge, and number of IV courses restarted for the same indication after IV-PO switch. All reported p-values were two-sided with the alpha set at a significance of 0.05.

RESULTS

In this study, 79 courses of antibiotics were recruited from 72 patients in pre-intervention phase, while 77 courses of antibiotics were recruited from 76 patients in post-intervention phase. The characteristics of the study samples were shown in Table 2. The most frequent site of infection is respiratory tract infection in both stages as shown in Table 2 (55.1% vs 61.0% in pre and post-intervention respectively). The type of antibiotics prescribed in both groups were as stated in Table 3, with amoxicillin-clavulanic acid being the most commonly prescribed antibiotic in both groups.

IV antibiotics were switched in a more timely fashion in the post-intervention group compared to the pre-intervention group ($p < 0.0001$). In the pre-intervention group, the mean difference in days between the actual switch and the days patients met criteria for a switch to oral therapy was 1.83 days ($SD = 1.55$), while in the post-intervention group the mean difference in days was 0.21 days ($SD = 0.59$) (Table 4).

In the post-intervention group, the mean duration of IV antibiotics was 2.81 days ($SD = 1.77$), which was significantly shorter than the pre-intervention group, with an overall

Table 4. Comparing outcome variables between pre and post intervention group

Variables	Pre- ^a (n=79) Mean (SD)	Post- ^b (n=77) Mean (SD)	Mean difference (95% CI)	t statistic (df)	p-value
Timeliness	1.83 (1.55)	0.21 (0.59)	1.63 (1.26: 2.00)	8.72 (100.87) ^c	0.000 ^c
Duration of IV antibiotics	4.05 (1.58)	2.81 (1.17)	1.23 (0.79:1.67)	5.54 (143.39) ^c	0.000 ^c
Mean length of hospital stay	5.53 (3.22)	4.09 (1.73)	1.44 (0.62:2.26)	3.49 (120.57) ^c	0.001 ^c
Antibiotics cost savings	13.10 (53.76) ^d	21.96 (23.23) ^e	-	-2.278 ^c	0.025 ^f

^a pre-intervention; ^b post-intervention; ^c independent t test; ^d median and interquartile range; ^e z statistic; ^f Mann-Whitney test

mean IV antibiotic duration in the ward of 4.05 days (SD=2.81) ($p<0.0001$). The most frequently used antibiotic for respiratory tract infection was amoxicillin-clavulanic acid. The overall consumption of IV amoxicillin-clavulanic acid decreased by 27.9% in the post-intervention group. For skin and soft tissue infections, cloxacillin was used most frequently, and post-intervention group had brought decrement in consumption of injection form by 21.7%. Cefuroxime was the most popular antibiotic for the treatment of urinary tract infection, and the pharmacist implemented antimicrobial stewardship strategies has brought down the consumption of IV cefuroxime by 46.5% (Table 4).

The length of hospital stay for patients in the post-intervention group was significantly shortened by 1.44 days compared to the pre-intervention group [4.09 days (SD=1.73) vs 5.53 (SD=3.22) days, $p=0.001$] (Table 4). The median antibiotic cost savings was significantly higher in the post-intervention group, which was [MYR 21.96 (IQR=23.23) vs MYR13.10 (IQR=53.76), ($p=0.025$)] (Table 4).

IV antibiotic courses switched to oral antibiotics on the day of criteria for switch met was significantly more in post-intervention group compared to pre-intervention group (88.3% vs 24.1%, $p<0.0001$). There was a significant reduction in the number of IV-PO switch that was only being performed upon discharge from the ward in the post-intervention group compared to pre-intervention group (31.2% vs 82.3%, $p=0.000$). There was no reinitiation of IV therapy after the early switch was made in both pre and post-intervention group. In the post-intervention group, doctors agreed on early switch on 75 out of 77 cases, which constitute 97.4% of acceptance rate of the intervention.

DISCUSSION

Our results had shown that implementation of pharmacist initiated printed AMS recommendations had significantly improved the timeliness of IV to oral antibiotic switch and shortened the duration of IV antibiotics in the ward. This finding was in accordance with the study by Dunn *et al.* conducted in Ireland, in which antimicrobials were switched in a more timely fashion in the intervention group ($n=92$) consisting of antimicrobial strategies such as application of stickers highlighting the patient was on IV antimicrobial and application of guidelines to the drug chart by the clinical pharmacists, compared to the pre-intervention group ($n=85$) where clinical pharmacists reviewed the drug charts and contacting prescribers to discuss a switch.¹⁹ Similar approach was implemented by McLaughlin *et al.*, who employed IV to oral switch therapy (IVOST) guidelines and a 'REFER TO IVOST PROTOCOL' stickers has reported improvement in the appropriateness of IV-PO switch timing in the post-intervention group

($n=107$) compared to pre-intervention group ($n=118$).¹⁶ These printed tools have growing importance as strategies to promote IV to oral antibiotic switch.

The significant reduction of length of hospital stay as well as medication cost savings from our study agreed with the study conducted by McLaughlin *et al.*, which reported reduction in length of hospital stay and antibiotic expenditure through the implementation of IVOST guidelines.¹⁶ A study conducted in Taiwan also showed that pharmacist-managed IV to oral switch service decreased the length of hospital stays as well as significant cost savings on both the medication costs and total inpatient expenditures.²⁴ The use of printed AMS interventions had helped to lessen the cost by shorter duration of IV and replaced with more consumption of cheaper oral dosage form.

In our study, there was no reinitiation of IV therapy due to relapse of infection after IV-PO switches were being made. Dunn *et al.*, which utilised similar interventional strategies in our study also reported only one case of reinitiation of IV antibiotic in the interventional phase. This proves the reliability of pharmacist initiated printed AMS recommendations in guiding switch decision. This result was also in concurrent with the study conducted by Mertz *et al.* that there was no significant increase in patients relapse in the intervention phase where a printed checklist of criteria for switching to oral antibiotics was used.¹⁵ The optimal time for switching to oral antibiotics is on days 2–4 of IV therapy, when the culture results and the initial clinical course allow a reassessment of the treatment plan.²⁵ Evidence from several studies had reported that once a patient's temperature is 37.8°C or less for 24 hours and he or she is otherwise stable, he or she can be switched to oral therapy as the subsequent risk of clinical deterioration is very low.²⁶

In the post-intervention stage, clinicians were required to provide reasons if they did not agree with pharmacist's recommendation on early switch. One of the doctors disagreed with early switch as patient's white blood cell level was 20.4×10^9 cells/liter, despite the fact that the white blood cell is trending downwards since admission. The patient was given full IV course in the ward before discharge. In fact, a guideline from the NHS Gloucestershire hospitals has suggested that absence of normal white cell count should not impede the switch if all other criteria are met and patients are not neutropenic.²⁷ In another case, the reasoning given by clinician for employing delayed switch was 'to keep another day of IV antibiotic'. This shows that some prescribers are more comfortable with maintaining full IV course. Some clinicians felt that patient was not ready to take PO antibiotics even though patient was ordered for other medications or food orally.²⁸ In our study, early switch was disagreed in another patient who

Table 5. Recommended switch (similar coverage) in our study		
IV antibiotics	Oral antibiotics	Bioavailability (%) ^{34,35}
Ampicillin	Amoxycillin	74-92
Amoxicillin-clavulanic acid	Amoxicillin-clavulanic acid	60
Benzylpenicillin	Phenoxymethylpenicillin /	60-73
	Amoxycillin	74-92
Ceftriaxone	Amoxicillin-clavulanic acid /	60
	Cefuroxime	60-90
Cefuroxime	Cefuroxime	60-90
Cloxacillin	Cloxacillin	35-76
Metronidazole	Metronidazole	>90
Ampicillin-sulbactam	Ampicillin-sulbactam	60-90
Azithromycin	Azithromycin	60-90

had history of severe community-acquired pneumonia with para-pneumonic effusion, despite patient meeting the IV-PO switch criteria in this current admission.

Another main obstacle limiting IV-PO switch was the belief that oral antibiotics do not achieve the same bioavailability as that of intravenous forms.²⁹ Moreover, they believed that chances of reinfection would be less if they give a complete IV course of antibiotics.²² As a result, physicians usually tend to opt for the IV medications at the time of admission and continue them till patient discharge. But the fact was that some antibiotics have good bioavailability when given orally (Table 5).^{30,31} In our study, we recommended the IV-PO switch for eligible patients based on suitable oral antibiotics with good bioavailability as shown in Table 5.

Limitations

One of the limitations of this study was that costs of drug preparation, administration, as well as pharmacist and nursing labour were not included in the analysis. We were not able to follow up the discharged patients longer than the hospital stay period, as there were no hospital electronic database where we can monitor if there were readmissions due to relapse after IV-PO antibiotic switches were made. Further study can be done to assess the impact of printed AMS recommendations towards hospital readmissions and mortality of the patients.

This study was a pre-post intervention study without the use of control group. This is a common quasi-experimental design which we aim to demonstrate causality between our intervention and the outcomes. Including a pre-intervention group could provide some information about what the outcome would have been if the intervention does not occurred. However, without the use of control

group, we could not deny the pre-existing factors and other confounders that might influence our results.

CONCLUSIONS

Printed AMS recommendations initiated by pharmacists had shown to improve the timeliness of IV-PO switch, reduce the duration of IV, reduce the length of hospitalisation, and increase antibiotic cost savings. It can be incorporated as one of the AMS strategies of the hospitals to encourage IV-PO antibiotics switch. Although our study involved printed AMS recommendations, this study can also apply to hospitals using electronic health record. Similar intervention can be created electronically such as electronic trigger tool and integrated in the electronic health records system.

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CONFLICT OF INTEREST

We attest that we have no financial or other relationships that could be construed as a conflict of interest for this study.

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