© 2021 Journal of Pharmacy & Pharmacognosy Research, 9 (5), 695-703, 2021
ISSN 0719-4250
http://jppres.com/jppres

Original Article

The effect of early switching from intravenous to oral antibiotic therapy: a randomized controlled trial

[El efecto del cambio temprano de la terapia con antibióticos intravenosos a orales: un ensayo controlado aleatorio]

Anh Dung Nguyen[1], Tuong-Anh Mai-Phan[1]*, Minh Hoang Tran[2], Hong Tham Pham[3]

[1]General Surgery Department, Nhan Dan Gia Dinh Hospital, Ho Chi Minh City, V-70000, Vietnam.
[2]Faculty of Pharmacy, University of Medicine and Pharmacy, Ho Chi Minh City, V-70000, Vietnam.
[3]Pharmacy Department, Nhan Dan Gia Dinh Hospital, Ho Chi Minh City, V-70000, Vietnam.
*E-mail: anhmpt@bvndgiadinh.org.vn

Abstract

Context: The benefit of early switching from intravenous (IV) to oral (PO) antibiotic therapy has been controversial during the last few decades.

Aims: To evaluate the effect of early switching from IV to PO antibiotics on treatment outcomes in surgical patients at one of the largest public hospitals.

Methods: Two hundred and nine patients admitted for a therapeutic antibiotic to orthopedic and general surgery conditions were randomly assigned into three groups: control (non-switching) (n = 69), early switching within 48-72 hours (n = 66), and late switching after 72 hours (n = 74). The rate of effectiveness, length of hospital stay, and cost were recorded and analyzed.

Results: Treatment effectiveness was not significantly different among the three groups. However, the length of stay and cost were found reduced in early switching group, with a decrease of 2-3 days of hospital stay and 30-40% of total healthcare spending compared to late or non-switching protocol ($p<0.001$).

Conclusions: Early switching does not compromise the outcome of antibiotic treatment while this protocol is superior to non-switching and late-switching in terms of length of hospital stay and cost of treatment. Early switching should be considered for surgery patients to optimize the treatment.

Keywords: antibiotic; effectiveness; intravenous-to-oral; switch therapy.

Resumen

Contexto: El beneficio del cambio temprano de la terapia con antibióticos intravenosos (IV) a orales (PO) ha sido controvertido durante las últimas décadas.

Objetivos: Evaluar el efecto del cambio temprano de antibióticos IV a VO sobre los resultados del tratamiento en pacientes quirúrgicos en uno de los hospitales públicos más grandes.

Métodos: Doscientos nueve pacientes ingresados para recibir un antibiótico terapéutico en condiciones de cirugía ortopédica y general fueron asignados aleatoriamente en tres grupos: control (sin cambio) (n = 69), cambio temprano dentro de las 48-72 horas (n = 66), y cambio tardío después de 72 horas (n = 74). Se registraron y analizaron la tasa de efectividad, la duración de la estancia hospitalaria y el costo.

Resultados: La efectividad del tratamiento no fue significativamente diferente entre los tres grupos. Sin embargo, se encontró que la duración de la estadía y el costo se redujeron en el grupo de cambio temprano, con una disminución de 2-3 días de estadía en el hospital y un 30-40% del gasto total en atención médica en comparación con el protocolo tardío o sin cambio ($p<0,001$).

Conclusiones: El cambio temprano no compromete el resultado del tratamiento con antibióticos, mientras que este protocolo es superior al no cambio y al cambio tardío en términos de duración de la estancia hospitalaria y costo del tratamiento. Se debe considerar el cambio temprano para que los pacientes quirúrgicos optimicen el tratamiento.

Palabras Clave: antibiótico; cambiar terapia; eficacia; intravenoso a oral.

ARTICLE INFO
Received: April 4, 2021.
Received in revised form: May 10, 2021.
Accepted: May 15, 2021.
Available Online: May 16, 2021.

INTRODUCTION

Antibiotics are widely used to treat infections. One-third of inpatients are given antibiotics, in which injection-based antibiotics comprises 40% (McLaughlin et al., 2005). However, intravenous (IV) antibiotics are not only more expensive than the oral (PO) antibiotics but also required more auxiliary equipment and preparation time, which can increase the cost by 13-113% (van Zanten et al., 2003). Recently, novel PO antibiotics with better bioavailability have offered healthcare providers options to switch from IV to PO.

A number of studies have confirmed the benefits of early switching antimicrobial therapy for both patients and the healthcare system (Vouloumanou et al., 2008; Mertz et al., 2009). The decline in the length of antibiotic treatment could reduce the risks of antibiotic resistance, *Clostridioides difficile* infection, acute kidney injury, and peripheral intravenous cannula infection. Moreover, patients could be discharged earlier with much more pleasure due to a decrease in length of stay and costs as well as hospital overcrowding (McCallum et al., 2013).

To date, many studies showed the great benefits of switching from IV to PO antibiotics in some infectious diseases, especially skin and soft tissue, urinary tract, respiratory tract, gallbladder, and biliary tract infection (von Gunten et al., 2003). Higher level of evidence is necessary to confirm the benefit of early switching protocol in infectious condition management. Therefore, this clinical trial was conducted to investigate the effectiveness and cost of IV-to-PO antibiotic switch therapy in some surgical infection conditions.

MATERIAL AND METHODS

Settings and participants

This randomized controlled trial aimed at evaluating the effectiveness of early switching protocol in surgical infection treatment. Adult patients admitted for skin and soft tissue infection (SSTI) at the Orthopedics Department and appendicular peritonitis (AP) at the General Surgery Department of Nhan Dan Gia Dinh Hospital, a public hospital in Ho Chi Minh City, Vietnam, from March to August of 2018, were recruited into the study.

All patients hospitalized in the study period and receiving IV antibiotic therapy for ≥2 days to treat SSTI and AP were selected for enrollment. Included patients were those who: (1) were being given IV antibiotics for the third day, (2) were able to take oral medications without difficulty, (3) had infection symptoms improved (white blood cells decreasing towards normal range, body temperature >36°C and <38°C for at least 24-48 hours, respiratory rate <20 breaths/ min, pulse <90 beats/min), (4) were prescribed oral antibiotics based on antimicrobial susceptibility testing.

Patients were excluded if they: (1) were under 18 years old, (2) were not eligible for oral antibiotic regimen (malabsorption, partial or total gastrectomy, short bowel syndrome, gastrointestinal obstruction, gastrointestinal bleeding, paralytic ileus, severe diarrhea, malignancy, patients in cardiac or intensive care unit), (3) had dysphagia or unconsciousness, (4) had conditions that require a prolonged course of intravenous antibiotics (osteomyelitis, meningitis, infection in prosthetic material, endocarditis, septic shock, severe cellulitis, pneumonia in AIDS patients, *Staphylococcus aureus*-induced sepsis, cirrhosis, evidence of *Pseudomonas* infection), (5) patients with immunodeficiency (leukopenia, cancer chemotherapy, organ transplantation, hyposplenism).

Patients were enrolled and randomly allocated into three groups: control group (non-switching), early switching group (IV-to-PO conversion within 48-72 hours), and late switching group (IV-to-PO conversion after 72 hours) by MS Excel 2010 (Microsoft, USA) with an allocation ratio of 1:1:1. Once being assigned, patients were kept blinded to the treatment they received. All the patients gave their informed consent.

Ethics approval statement

This study was approved by the Ethics Committee of Nhan Dan Gia Dinh Hospital, Ho Chi Minh City, Vietnam, under approval number 50/CN-HĐĐĐ, on 16 May 2018. This trial was also registered at clinicaltrials.gov (ID NCT04781439).

Intervention

The intervention was carried out using three types of IV-to-PO conversions: (1) sequential therapy (replacing the parenteral form with its oral counterpart); (2) equivalent switch therapy (shifting to an oral antibiotic of the same class with equivalent spectrum); (3) step down therapy (converting to an oral agent in another class or to a different medication of the same class where the frequency, dose, or spectrum may not be the same (Quap, 2018). Decisions on type of conversions for patients were left to the attending physicians.

Outcomes

The primary outcome was effectiveness of the infection treatment, with the signs of infection as the measure, including: (1) body temperature ≥38^{o}C or <36^{o}C; (2) pulse >90 beats/min; (3) respiratory rate >20 breaths/min; (4) white blood cells >12.10^{9}/L or <4.10^{9}/L. Patients with two or more symptoms above were marked as treatment failure. The assessment was noticed when patients were discharged and at their first follow-up visit (five days after discharge). The secondary outcomes were length of hospital stay (days) and cost of treatment (Vietnam dong). Treatment costs were measured using direct healthcare costs, including antibiotics and auxiliary equipment (injection solvents, syringes, needles, infusion sets, threaded needles, injection stoppers, adhesive bandages).

Statistical analysis

The data were described using frequency and percentage for qualitative measurements and mean and standard deviation for quantitative measurements. Winsorization method was used to deal with outliers (Chambers et al., 2000). Continuous variables were checked for normality using Shapiro-Wilk test and were presented as mean with standard deviation (mean ± SD). Mann-Whitney U test or Kruskal-Wallis test was used to compare the mean between or among groups of variables with non-normal distribution while the comparison of proportions was made using Chi-Square test. Adjusted mean comparison was performed using one-way ANCOVA. Statistically significant level was at 0.05. All data analyses were conducted using Stata 14 (Stata Corp, College Station, Texas, USA).

RESULTS

Participant characteristics

Two hundred and nine patients with SSTI and AP (135 men, 74 women) were recruited for the study, the average age was about 36 years, as shown in Fig. 1A and Fig. 1B.

Table 1 describes the characteristics of patients in three groups. Similarity was found in three groups in the distribution of sex, age, and diagnosis, respectively.

Types of IV-to-PO conversion

Fig. 2 depicts the proportions of the three main types of conversion. At the Trauma and Orthopedics Department, where SSTI patients were treated, equivalent switch and step down therapy were widely applied for approximately 90% of participants. In contrast, patients with AP at the Surgical Gastroenterology Department were primarily indicated sequential therapy with 63.73% cases.

Outcomes

Effectiveness assessment

The treatment success rates among the groups were not significantly different (p>0.05), with all the proportions greater than 80% (Table 2). In case of treatment failure, doctors would develop an appropriate solution for that patient depending on the severity of the infection.

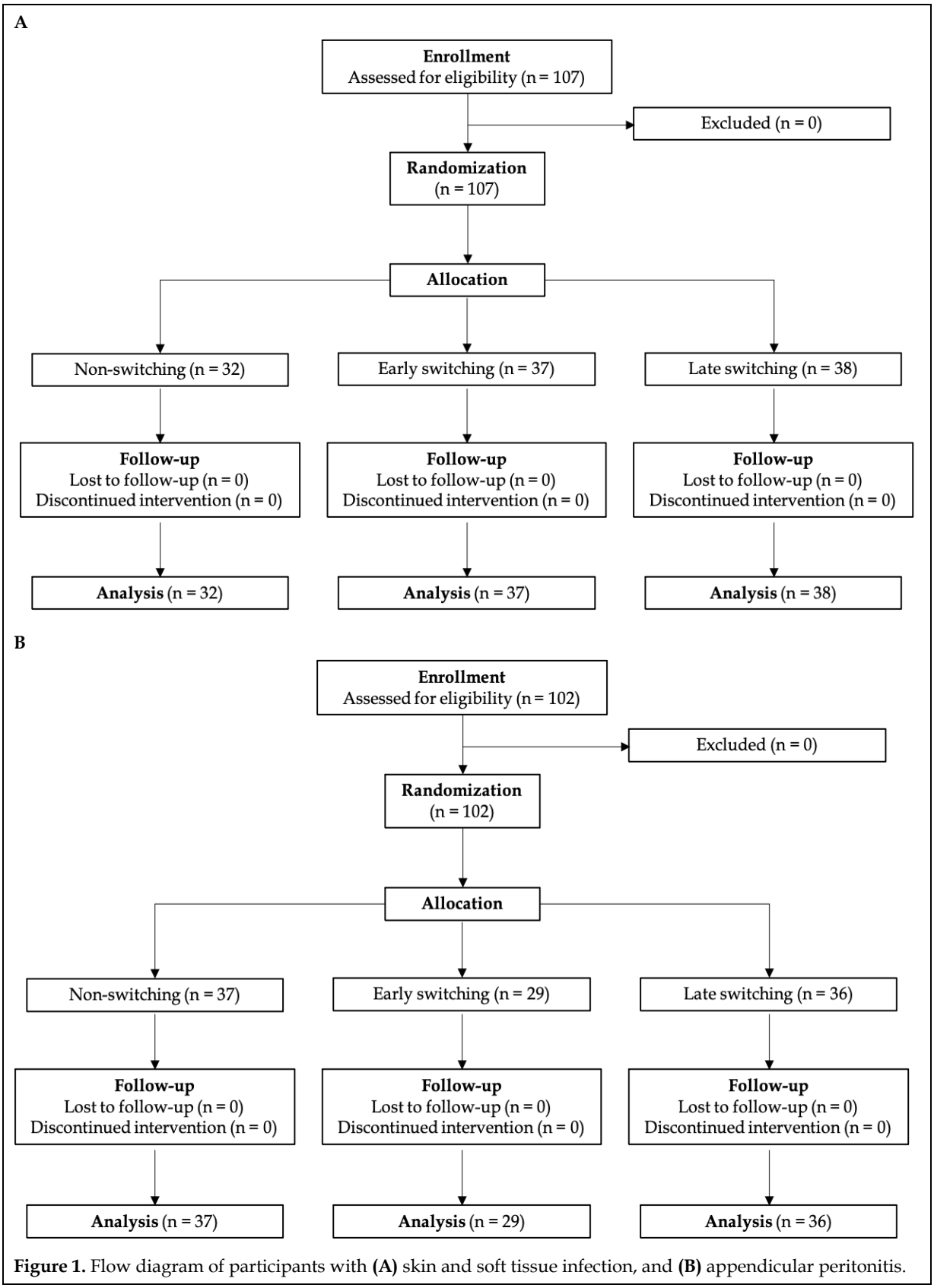

Figure 1. Flow diagram of participants with **(A)** skin and soft tissue infection, and **(B)** appendicular peritonitis.

Table 1. Characteristics of the participants.

Variable	Control N (%)	Early switching N (%)	Late switching N (%)
Diagnosis N *(%)*			
SSTI (n = 107)	32 (29.91)	37 (34.58)	38 (35.51)
AP (n = 102)	37 (36.27)	29 (28.43)	36 (35.29)
Age N (mean ± SD)			
SSTI	36.25 ± 11.75	36.49 ± 16.16	38.42 ± 14.17
AP	41.54 ± 15.30	33.34 ± 14.22	37.78 ± 13.58
Male/Female			
SSTI	27/5	31/6	20/18
AP	22/15	15/14	20/16

SSTI: skin and soft tissue infection, AP: appendicular peritonitis; SD: standard deviation. The participants had an average age of 37.3. In SSTI patients, the average age between male and female were similar (34.7 and 34.0). In AP patients, these figures were 36.3 and 39.9, respectively. The proportions of male/female were 64.6%/35.4%.

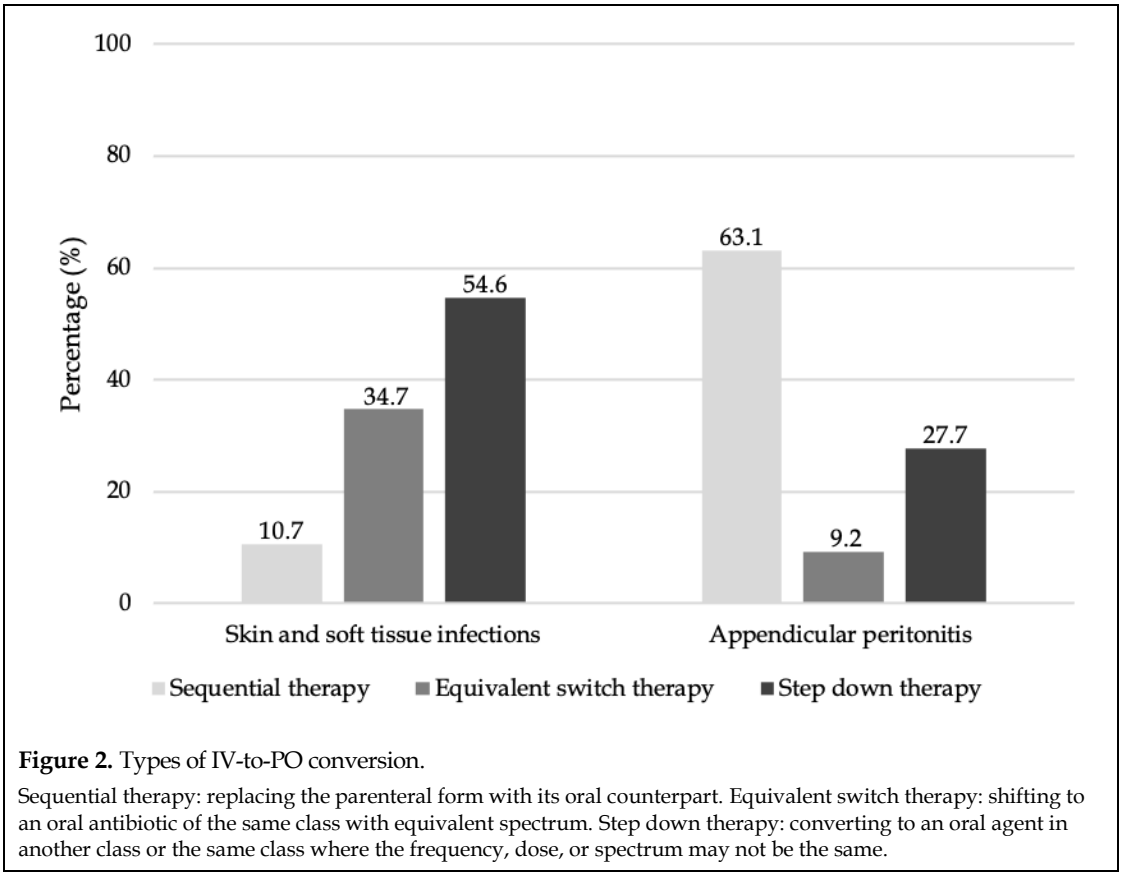

Figure 2. Types of IV-to-PO conversion.

Sequential therapy: replacing the parenteral form with its oral counterpart. Equivalent switch therapy: shifting to an oral antibiotic of the same class with equivalent spectrum. Step down therapy: converting to an oral agent in another class or the same class where the frequency, dose, or spectrum may not be the same.

Table 2. The effectiveness of the switch therapy.

Variable	Treatment success N (%)	p-value
SSTI		
Control	27 (84.38)	
Early switching	31 (83.78)	0.926[a]
Late switching	33 (86.84)	
AP		
Control	31 (83.78)	
Early switching	25 (86.21)	0.945[a]
Late switching	30 (83.33)	

[a]Chi-Square Test. SSTI: skin and soft tissue infection, AP: appendicular peritonitis; SD: standard deviation.

Table 3. Expenditures on antibiotic therapy and entire treatment.

Variable	Antibiotic cost*		Entire cost*	
	Mean ± SD	p-value	Mean ± SD	p-value
SSTI				
Control	286.69 ± 99.96		10727 ± 7393	
Early switching	199.09 ± 97.61	<0.001[b]	6494 ± 3048	<0.001[b]
Late switching	310.58 ± 151.63		9937 ± 6727	
AP				
Control	883.16 ± 231.93		7903 ± 1201	
Early switching	591.56 ± 169.58	<0.001[b]	5674 ± 848	<0.001[b]
Late switching	840.40 ± 323.59		7318 ± 1136	

*Currency unit: 1000 Vietnam dong (0.043 USD). [b]one-way ANCOVA Test. SSTI: skin and soft tissue infection, AP: appendicular peritonitis; SD: standard deviation.

Cost of treatment and length of hospital stay

Expenses on the antibiotic therapy and the entire treatment are described in Table 3. The average cost in antimicrobial utilization and entire treatment of the three groups differed significantly (p<0.001). Participants in the early switching group had the lowest expenditures in both antibiotic therapy and entire treatment, less than about 30-40% compared to those receiving late or non-switching therapy.

Regarding the length of hospital stay of the patients, in both infections, early switching group had the lowest average length of stay (3.43 days for SSTI and 4.86 days for AP, respectively). The differences compared to control and late switching groups were statistically significant (p<0.001), with a decrease of 2-3 days of hospitalization (Table 4).

DISCUSSION

As far as is known, there is little evidence in the scientific literature to support the implementation of early switching protocol, especially in developing countries. In this study, there was no difference in treatment success rate among non-switching, early switching, and late switching patients. The results were consistent with previous publications (Adibe et al., 2008; Mertz et al., 2009). Coupled with those previous studies, this study's findings indicated that early switching protocol is not inferior to non-switching and late switching therapy.

Table 4. Length of hospitalization.

Variable	Length of stay (days)	
	Mean ± SD	p-value
SSTI		
Control	7.69 ± 4.03	
Early switching	3.43 ± 0.93	<0.001[b]
Late switching	8.05 ± 3.90	
AP		
Control	7.24 ± 1.16	
Early switching	4.86 ± 0.92	<0.001[b]
Late switching	6.56 ± 0.99	

[b]one-way ANCOVA Test. SSTI: skin and soft tissue infection, AP: appendicular peritonitis; SD: standard deviation.

Additionally, the switch protocol implementation has shortened the length of IV antibiotic use. However, the variation of this decline depends on an early or late conversion. This finding is similar to result in previous studies (Mertz et al., 2009). The decrease in IV duration was shown to be beneficial to both patients and medical staff, including reducing the risks of IV therapy, the cost of treatment, and the burden of care on healthcare workers (Mertz et al., 2009; Cyriac and James, 2014).

Regarding the length of stay, while some studies showed an increase in hospital stay when implementing the switching therapy (Mertz et al., 2009), this research and prior publications showed that early switching regimen had reduced the length of stay compared to non-switching therapy (McLaughlin et al., 2005; Cyriac and James, 2014). Mertz et al. (2009) showed that the length of IV use was shorten but the overall length of stay was not reduced because of case-mix of patient in medical wards requiring further workup or involving concomitant medical conditions.

In terms of cost, for patients with an early conversion, there was a decrease of 30-37% in antibiotic expenditures and another 30-40% in the total cost, compared to non-switching patients'. These results reflected a consistency with various studies (Adibe et al., 2008; Cyriac and James, 2014; Eckmann et al., 2014), yielding more evidence for the implementation of early switching from IV to oral medication. To maximize the effectiveness, to save cost as well as to reduce length of stay, the early IV-to-PO switching protocol should be prioritized.

To maximize the effectiveness, save cost as well as reduce length of stay, the early IV-to-PO switching protocol should be allocated. However, further research with larger scales needs to be conducted to precisely evaluate the conversion's effectiveness and safety, including adverse medication reaction, recurrence, and re-admission rate within 90 days after discharge. Additionally, more studies in more infectious diseases should also be carried out to provide more apparent evidence for implementing the early switching protocol.

Despite these findings, this study still has certain limitations. First, assessments of treatment effectiveness, length of hospital stay, length of IV antibiotic use, and patients' cost savings were carried out over a small sample. Second, the study did not investigate the safety of the switch therapy, which might be a limit to the implementation of the conversion. Third, evaluation of the therapy did not cover all the advantages of the antibiotic switching protocol, including a lessening in the workload of healthcare workers, reducing the risks of medication administration (secondary infection, anaphylaxis, phlebitis).

CONCLUSIONS

The outcome of antibiotic treatment for SSTI and AP is not different in three groups. However, reduction in length of hospital and cost for the treatment were observed in the early switching group.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

ACKNOWLEDGMENTS

The research team would like to give thanks to the staff of Nhan Dan Gia Dinh Hospital for having assisted during the data collecting process.

REFERENCES

Adibe OO, Barnaby K, Dobies J, Comerford M, Drill A, Walker N, Mattei P (2008) Postoperative antibiotic therapy for children with perforated appendicitis: long course of intravenous antibiotics versus early conversion to an oral regimen. Am J Surg 195(2): 141–143.

Chambers R, Kokic P, Smith P, Cruddas M (2000) Winsorization for Identifying and Treating Outliers in Business Surveys. Proceedings of the Second International Conference on Establishment Surveys, Alexandria, Virginia: American Statistical Association, pp. 717–726.

Cyriac JM, James E (2014) Switch over from intravenous to oral therapy: A concise overview. J Pharmacol Pharmacother 5(2): 83–87.

Eckmann C, Lawson W, Nathwani D, Solem CT, Stephens JM, Macahilig C, Simoneau D, Hajek P, Charbonneau C, Chambers R, Li JZ, Haider S (2014) Antibiotic treatment patterns across Europe in patients with complicated skin and soft-tissue infections due to meticillin-resistant Staphylococcus aureus: a plea for implementation of early switch and early discharge criteria. Int J Antimicrob Agents 44(1): 56–64.

McCallum AD, Sutherland RK, Mackintosh CL (2013) Improving antimicrobial prescribing: implementation of an antimicrobial i.v.-to-oral switch policy. J R Coll Physicians Edinb 43(4): 294–300.

McLaughlin CM, Bodasing N, Boyter AC, Fenelon C, Fox JG, Seaton RA (2005) Pharmacy-implemented guidelines on switching from intravenous to oral antibiotics: an intervention study. QJM 98(10): 745–752.

Mertz D, Koller M, Haller P, Lampert ML, Plagge H, Hug B, Koch G, Battegay M, Flückiger U, Bassetti S (2009) Outcomes of early switching from intravenous to oral antibiotics on medical wards. J Antimicrob Chemother 64(1): 188–199.

Quap CW (2018) Chapter 31: Intravenous to Oral Therapy Conversion. In: Murdaugh LB (ed), Competence Assessment Tools for Health-System Pharmacies. Bethesda MD, USA: ASHP Publications.

van Zanten ARH, Engelfriet PM, van Dillen K, van Veen M, Nuijten MJC, Polderman KH (2003) Importance of nondrug costs of intravenous antibiotic therapy. Crit Care 7(6): R184.

von Gunten V, Amos V, Sidler AL, Beney J, Troillet N, Reymond JP (2003) Hospital pharmacists' reinforcement of guidelines for switching from parenteral to oral antibiotics: a pilot study. Pharm World Sci 25(2): 52–55.

Vouloumanou EK, Rafailidis PI, Kazantzi MS, Athanasiou S, Falagas ME (2008) Early switch to oral versus intravenous antimicrobial treatment for hospitalized patients with acute pyelonephritis: a systematic review of randomized controlled trials. Curr Med Res Opin 24(12): 3423–3434.

AUTHOR CONTRIBUTION:

Contribution	Nguyen AD	Mai-Phan TA	Tran MH	Pham HT
Concepts or ideas	x	x		x
Design	x	x	x	x
Definition of intellectual content	x	x		x
Literature search	x	x	x	x
Clinical trial	x	x		
Experimental studies	x	x		
Data acquisition	x	x		
Data analysis	x	x	x	x
Statistical analysis	x	x	x	x
Manuscript preparation	x	x	x	x
Manuscript editing	x	x	x	x
Manuscript review	x	x	x	x

Citation Format: Nguyen AD, Mai-Phan TA, Tran MH, Pham HT (2021) The effect of early switching from intravenous to oral antibiotic therapy: a randomized controlled trial. J Pharm Pharmacogn Res 9(5): 695–703.