Comparison between the Efficacy of Switch Therapy and Conventional Therapy in Pediatric Community-Acquired Pneumonia

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Objective: *Compare the treatment outcomes of switch therapy and conventional therapy in pediatric patients aged one month to five years old, diagnosed with community-acquired pneumonia who required hospitalization.*
Material and Method: *The present study was performed and approved by the Siriraj Research Ethics Committee. With informed consent, 57 patients who fitted the inclusion criteria were randomized into two groups, 1) the switch therapy group (SWT), who switched their method of receiving antibiotics from IV to oral within 24 hours after clinical improvement and body temperature under 37.8°C at least eight hours, and 2) the control group, the group treated as routine general practice. Chi-square tests, Fisher's exact tests, unpaired t-tests, and Mann-Whitney U tests were used in analysis. A non-inferiority analysis to estimate 1-sided 95% CIs was performed to determine the greatest difference (worst case) between groups.*
Results: *There were no significant differences in age, sex, clinical presentations, and antibiotics provided between the two groups. A statistically significant reduction in length of hospital stay was found in the SWT group ($p = 0.019$), whereas the readmission rate for both groups was not significantly different ($p = 0.66$). Morbidity and mortality were not found in either groups. The SWT group demonstrated non-inferior efficacy comparing to control group (difference 20%; $p<0.001$).*
Conclusion: *In pediatric community-acquired pneumonia, early switching from administer IV antimicrobial agents to oral form when clinical signs improved were safe and effective. Switch therapy showed non-inferiority outcomes compared to conventional therapy, and had advantages in shortening the length of stay and indirectly lowering the cost of hospitalization.*

Keywords: *Switch therapy, Pediatric pneumonia, Non-inferiority, Childhood pneumonia, Community acquired pneumonia*

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Although the overall mortality rate of community-acquired pneumonia (CAP) in children has declined over the past decade, it was one of the leading causes of death in children age under five year in Thailand[1,2]. In general, CAP patients have been treated as ambulatory cases due to improvement in accessibility of the health care system. However, approximately 10% of the cases required hospitalization[1]. Moreover, this disease has burdened the Thai economy with the high cost of care. Many studies evaluated the cost effectiveness and clinical outcome of the new approaches to treatment, including early switching from parenteral antimicrobials to oral administration[3]. Studies in adult populations demonstrated that early switching from parenteral to oral antimicrobials was safe, shortened the length of hospital stays, increased patient satisfaction, and showed cost-effectiveness[4,5]. Similarly, Athanassa et al found that in cases of moderate to severe CAP, switching early from intravenous administration of antibiotics to oral administration was safe and resulted in an earlier discharge[6]. This study was a meta-analysis selected randomized controlled trial (RCT) study that defined "early switching" as giving patients intravenous antibiotics for at least two days and then changing to an oral form when clinical improvement is seen. No differential treatment success was observed in this study between the early switching and conventional treatment groups. Additionally, their results were similar to previous non-RCT studies[7]. As such, switch therapy showed enough evidence-based promised to encourage clinicians to follow this practice in adult patients. However, this same evidence for early-switch therapy in the pediatric population is limited. In Thailand, management of hospitalized children diagnosed with CAP generally follows the guidelines

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of the Thai Association of Pediatric Respiratory and Critical Care Medicine, which established the criteria for switching antibiotics when patients were clinically improving. Switch antibiotics still depended on clinical judgment and physicians' preference. In general practice, for safety and compliancy reasons, patients were required to stay in the hospital for at least 24 hours for observation after switching to oral administration of antibiotics. Importantly, no studies on early switching to oral antibiotics and early discharge guidelines for pediatric CAP has been performed in Thailand. Therefore, the present study was conducted to compare the efficacy of switching early from intravenous to oral antibiotics to that of conventional treatment in patients with pediatric community-acquired pneumonia. Our hypothesis was that switch therapy would result in comparable efficacy to conventional therapy regarding safety and readmission rate.

Material and Method

Study setting and participants

The present study was a pilot prospective randomized control trial, based in a teaching hospital. The study site was the Department of Pediatrics of Siriraj Hospital in Bangkok, Thailand, a primary and tertiary care center with 288 pediatric beds (excluding newborns). The study period was between June 2009 and May 2012.

Participants were children with no underlying diseases, aged one month to five years old and diagnosed with pneumonia, (at least two criteria from age-specific cut-offs for increased respiratory rates, chest retraction, respiratory distress, and abnormal chest radiography). Participants required systemic intravenous antibiotics during in-patient service and were able to be treated as out-patients after switching antibiotics. We excluded patients who were admitted to the pediatric intensive care unit, had contraindication for oral antibiotic treatment, were diagnosed with nosocomial pneumonia, or had abnormal gastrointestinal absorption. The enrollment areas were the two general pediatric wards for small children aged ≤5 years old. After giving informed consent, each participant was randomized into two groups (intervention and control). We used computer to randomly assign subjects and kept the assignment in sealed envelopes to ensure secrecy.

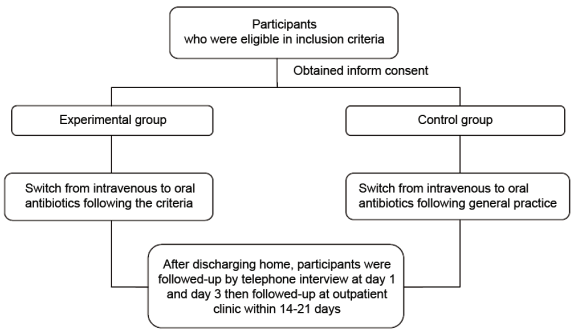

Fig. 1 Flow diagram of selected randomized controlled trials (RCTs).

Study intervention

The subjects in the control group (CT) were treated with the standard medical procedures for pneumonia, which included switching from IV-administered antibiotics to oral administration at least 48 hours after the patient's fever had dissipated. The subjects in the experimental group, or, switch therapy group (SWT), were treated with standard medical care as well but when their core body temperature dropped below 37.8°C for at least eight hours and their clinical signs were stable, early switching the IV to the oral antibiotics was performed. Patients were evaluated before the switch to ensure that their gastrointestinal tracts, function were normal. Other standards of care, including nursing care, medical care, and rehabilitation process provided were not significantly different from that of the control group.

Baseline, follow-up, and outcome measurements

Patients in both groups were monitored throughout their hospitalization. After discharge, two telephone follow-ups were performed by trained nurses on day 1 and day 3 post-discharge. Appointments were made for participants to have a check-up within two to three weeks post-discharge.

Data collection

Data collection included demographic information, vaccination histories, family history of allergies, smokers in the household, signs and symptoms during hospitalization, treatment regimens, length of stay, complications after discharge, and followed-up information were recorded.

Statistical analysis

The measurement outcomes of the present study were the readmission rate, length of hospital stay, and mortality rate. Chi-squared tests, Fisher's exact tests, Mann-Whitney U tests, and non-inferiority tests were performed to compare the outcomes of both groups with statistical significance set at $p<0.05$. Data

was analyzed using SPSS version 18 (Inc.; Chicago, Illinois).

Results

During the study period, 57 patients diagnosed with community-acquired pneumonia were voluntarily enrolled in the study and completed the protocol. Of those, 26 participants were randomly selected for the intervention group. Siriraj Hospital is a tertiary care institution and most in-patient cases had underlying diseases and were not eligible for enrollment. The demographic data was shown in Table 1. There were no differences in mean age, sex, clinical presentations, and history. Table 2 represented the clinical outcomes. Means length of hospital stay in intervention group was significantly lower than control group ($p = 0.019$). Both groups had the same readmission rate; however, the diagnosis of readmission in the intervention group was diarrhea, in contrast to the control group, which was pneumonia. There was no fatal case and no complications of treatment for pneumonia. The most popular IV and oral antibiotics were third generation cephalosporin similarity. Switch parenteral to oral antibiotics within 24 hours after afebrile was non-inferior to general practice (difference, 20%; $p<0.001$).

Discussion

It has been highlighted that switching from IV-administered antibiotics to oral administration after afebrile at least eight hours in hospitalized patients

Table 1. Baseline clinical manifestations of participants

Characteristics	SWT group (n = 26), n (%)	CT group (n = 31), n (%)	*p*-value
Male	11 (42.3)	19 (61.3)	0.15
Age (months), mean ± SD	16.4±13.30	14.7±13.34	0.11
Clinical presentation at baseline			
Temperature (°C), mean ± SD	38.0±0.82	38.1±1.07	0.47
Respiratory rate (/min), mean ± SD	48.8±10.80	51.0±7.55	0.30
% oxygen saturation, mean ± SD	94.7±3.84	95.4±2.03	0.88
Dyspnea	10 (38.5)	18 (58.1)	0.14
Tachynea	16 (61.5)	23 (74.2)	0.31
Cyanosis	2 (7.7)	1 (3.2)	0.59
Retraction	19 (73.1)	20 (64.5)	0.57
Sign of dehydration	14 (53.8)	22 (71.0)	0.18
History of immunization			
Seasonal influenza	0 (0)	1 (3.2)	1.00
Conjugated Pneumococcal	2 (7.7)	4 (12.9)	0.68
Haemophillus influenza	0 (0)	1 (3.2)	1.00
History of smoking	17 (65.4)	15 (48.4)	0.20
History of allergy	5 (19.2)	0 (0)	0.16

SWT = switch therapy; CT = control

* $p<0.05$ is defined as statistical significance

Table 2. Clinical outcomes during admission and readmission rate

Clinical outcomes	SWT group, n (%)	CT group, n (%)	*p*-value
Length of hospital stay (days), mean ± SD	3.81±1.6	4.77±1.5	0.019*
Duration of IV antibiotics (hours), mean ± SD	20.85±20.8	24.45±37.8	0.130
Initial IV antibiotics			
3rd generation cephalosporin	22 (84.6)	30 (96.8)	0.167
Oral antibiotics			0.495
3rd generation cephalosporin	10 (38.5)	7 (22.6)	
Amoxycillin/amoxicillin-clavulonic	12 (46.2)	17 (54.8)	
Others	4 (15.4)	7 (22.6)	
Readmission within 30 days after discharge	1 (3.8)	2 (6.5)	1

* $p<0.05$ is defined as statistical significance

with CAP was safe and shorten LOS. Moreover, it showed an advantage of early discharge without any adverse effect on the patient care. Our population had no morbidity and mortality from a new practice, as well as no harm to clinical management. Most previous studies in switch therapy were done in adult, in-patients services, and less likely to perform in children. Interestingly, the results in our study were similar to prior researches especially clinical outcomes[4]. Only one patient readmitted after discharge home in SWT group and was finally diagnosed with acute diarrhea, in contrast to CT group, which two patients were both definitely diagnosed with pneumonia for the second admission within 28 days. It has been implied that there was no treatment failure in SWT group even it was not shown significant in statistics. The majority of parenteral antibiotics were third generation cephalosporin, which was similar to prior study in pediatric pneumonia[8]. In Thailand, the management of community-acquired pneumonia in infants and children older than three months of age based on the clinical practice guidelines by the Pediatric Infection Diseases Society and the Infectious Diseases Society of America both recommended the empirical parenteral antibiotics with a third-generation cephalosporin for children who were not immunized of the pneumococcal vaccines[9]. As our population, only six patients had been vaccinated with conjugated pneumococcal vaccine and one with HIB vaccine, which protected against concerning causative organisms in bacterial CAP[10]. The duration of IV antibiotics were not statistically significant different between the groups since, during the study, physicians who treated patients in our study were mostly from the same group. It was possible that they observed and considered that the novel practice was no harm and were able to do under close monitoring. Moreover, it was explained that the CT group had been treated with IV antibiotics for a period of time depending on the clinical of patients and physicians' judgment. Therefore, the physicians changed their practice, to similar to our intervention, after the protocol was established. Our study had addressed the innovative strategy by maximizing the hospital resources and ultimate cost of patient care, which finally contributed to promote the cost effectiveness under the economic policy. Thailand has been faced with high economic burden, which undoubtedly influences health care provider to practice in the higher level of medical care but minimize the utility cost; therefore, shortening length of hospital stay under standard of care would be one of the best solutions for in-patients service. It could be attributed to the fact that the one way to lower cost of treatment for pediatric pneumonia was to early discharge with followed-on, and early transition to oral antibiotics[11,12].

A limitation of the present study was that it had been done in general ward in tertiary care hospital. Therefore, the number of cases that were eligible in the inclusion criteria was lower than expectation. Many patients did not fit the criteria since most of them were complicated and had underlying diseases. However, a generalization in our population should be considered.

Conclusion

In pediatric community-acquired pneumonia, early switching from IV-administered antibiotics to oral administration when clinical improved and providing ambulatory follow-up were safe and effective. Our study showed non-inferiority from conventional therapy. Furthermore, it had the advantage of shortening the length of stay, which indirectly lower the cost of treatment. This new practice should be implemented in clinical practice guideline, particularly in the setting that financial problems was concerned.

What is already known on this topic?

Management of pediatric community-acquired pneumonia proved that early switching parenteral to oral antibiotics when clinical improved were safe. Many studies showed the advantages of early switching particularly reducing cost of treatment. However, there has been no strong evidence in children that early switch therapy should be recommended.

What this study adds?

Early switching from parenteral to oral antibiotics when clinical improved in hospitalized children diagnosed with CAP was no harm comparing to previous practice. Conversely, it had the benefit in shortening length of stay and cost of treatment.

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Authors contributions

All authors read and approved the final manuscript. SI, as the primary investigator, conducted the protocol, enrolled the participants, participated in data analysis, and contributed to drafting the manuscript. Winijkul G and Sonjaipanich S were the co-investigators and enrolled the participants. Manaboriboon B conceived of the study, participated in data analysis, and revised the manuscript for the intellectual content.

Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบประสิทธิผลการเปลี่ยนยาปฏิชีวนะชนิดฉีดเป็นชนิดกินตามข้อบ่งชี้กับตามแนวทางเวชปฏิบัติในผู้ป่วยเด็กที่ได้รับการวินิจฉัยเป็นโรคปอดบวม

สุภิญญา อินอิว, กรมิกา วินิจกุล, สุประพัฒน์ สนใจพาณิชย์, บุญยิ่ง มานะบริบูรณ์

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบประสิทธิผลการเปลี่ยนยาปฏิชีวนะชนิดฉีดเป็นชนิดกินตามข้อบ่งชี้ของการศึกษากับตามแนวทางตามเวชปฏิบัติทั่วไปในผู้ป่วยเด็กอายุ 1 เดือน ถึง 5 ปี ที่ได้รับการวินิจฉัยเป็นโรคปอดบวมที่นอนรักษาตัวในโรงพยาบาล*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาทดลองแบบสุ่มและผ่านการรับรองจากคณะกรรมการจริยธรรมในคน คณะแพทยศาสตร์ศิริราชพยาบาล ผู้เข้าร่วมการศึกษาทั้งหมด 57 ราย ได้รับความยินยอมจากผู้ปกครอง โดยทั้งหมดถูกสุ่มออกเป็นสองกลุ่ม โดยกลุ่มทดลองเป็นผู้ป่วยที่รับการรักษาโดยการเปลี่ยนยาปฏิชีวนะชนิดฉีดเป็นชนิดกินตามข้อบ่งชี้คือ หลังไข้ต่ำกว่า 37.8 องศาเซลเซียสอย่างน้อย 8 ชั่วโมง สามารถเปลี่ยนยาปฏิชีวนะจากชนิดฉีดเป็นชนิดกินภายใน 24 ชั่วโมง กลุ่มควบคุมเป็นผู้ป่วยที่ได้รับการรักษาตามแนวทางเวชปฏิบัติทั่วไปคือ สามารถเปลี่ยนยาปฏิชีวนะชนิดฉีดเป็นชนิดกินตามความเห็นของแพทย์ผู้รักษา ผลของการศึกษาดูจากอัตราการกลับมานอนรักษาตัวในโรงพยาบาลภายใน 30 วัน ระยะเวลาในการนอนโรงพยาบาลและอัตราการเสียชีวิต โดยใช้ค่าทดสอบทางสถิติการทดสอบไคสแควร์ การทดสอบของฟิชเชอร์ การทดสอบค่าที การทดสอบของแมนน์วิทนีย์ และการทดสอบการเปรียบเทียบในแบบไม่ด้อยกว่า*

ผลการศึกษา: *การศึกษานี้ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของอายุ เพศ อาการแสดง ชนิดของยาปฏิชีวนะ อัตราการกลับมานอนรักษาตัวในโรงพยาบาล และอัตราการตายระหว่างกลุ่มทดลองและกลุ่มควบคุม แต่พบว่าระยะเวลาในการนอนโรงพยาบาลของกลุ่มทดลองน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ($p = 0.019$) นอกจากนี้ผลการรักษาในกลุ่มทดลองพบว่าไม่ด้อยไปกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติเช่นกัน (difference 20%; $p<0.001$)*

สรุป: *การรักษาผู้ป่วยเด็กที่ได้รับการวินิจฉัยเป็นโรคปอดบวมโดยการเปลี่ยนยาปฏิชีวนะชนิดฉีดเป็นชนิดกินเมื่อไข้ลงภายใน 24 ชั่วโมง พบว่ามีความปลอดภัย ให้ประสิทธิผลที่ดี และไม่ด้อยไปกว่าการรักษาตามแนวเวชปฏิบัติทั่วไป ทั้งยังสามารถลดระยะเวลาในการนอนโรงพยาบาลทำให้ประหยัดค่าใช้จ่ายในการรักษาเช่นกัน*