Infectious disease team review using antibiotic switch and discharge criteria shortens the duration of intravenous antibiotic: A single-center cluster randomized controlled trial in Thailand

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Key point

Infectious disease team review using antibiotic (ATB) switch and discharge criteria did not reduce the duration of intravenous (IV) antibiotic or length of hospital stay among overall patients; however, the duration of ATB was significantly reduced in non-sepsis patients in the intervention group.
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Abstract

Background: Strategies have been recommended to optimize early antibiotic (ATB) switching from intravenous (IV) to oral ATB. This study aimed to determine whether infectious disease (ID) team review using ATB switch and discharge criteria would shorten the duration of IV antibiotic and length of hospital stay (LOS).

Methods: This cluster randomized controlled trial was conducted in 8 general medical wards as cluster units at Siriraj Hospital during January-October 2019. ID team review with checklist criteria was performed on the third, fifth, and seventh day of IV-ATB treatment to determine the suitability of switching to oral ATB or outpatient parenteral ATB therapy, and early discharge for patients receiving IV-ATB versus control. The primary outcomes were LOS and the duration or days of therapy (DOT) or defined daily dose (DDD) of IV-ATB therapy.

Results: Four wards each were randomly assigned to the intervention and control groups (46 patients/cluster, 184 patients/arm). No significant difference was observed between intervention and controls for median duration of IV-ATB therapy (7 vs. 7 days) and LOS (9 vs. 10 days). A significantly shorter duration of IV-ATB was observed in patients without sepsis in the intervention group when measured by DOT (7 vs. 8 days, p=0.027) and DDD (7 vs. 9 days, p=0.017) in post-hoc analysis.

Conclusions: ID team review using checklist criteria did not result in a shorter duration of IV-ATB and LOS in overall patients. Further study is needed to determine if faster culture turnaround time or advanced testing will reduce the duration of IV-ATB therapy.

Keywords: Antibiotic switch; checklist criteria; early discharge; shortening; randomized controlled trial
Introduction

Hospitalized patients with infections generally receive intravenous (IV) antibiotic (ATB) therapy. However, the available evidence suggests that IV ATBs are frequently unnecessary and may cause harmful complications, such as line-related infection or injury and prolonged length of hospital stay (LOS) [1]. Administration of IV ATBs is essential in critically ill patients, such as those with septic shock [2]; those who have specific site of infection that requires IV ATBs, such as meningitis [3]; or, when microbial susceptibility testing shows the effectiveness of only an IV ATB agent. Multiple antimicrobial stewardship programs (ASPs) have been designed to improve the appropriate use of ATBs by promoting the selection of the optimal antimicrobial regimen, the best route of administration, and the optimal duration of ATB treatment [4]. Hospital ASP could increase infection cure rates while reducing adverse effects, hospital costs, and LOS [5]. Early switching (ES) from IV to oral ATB therapy is one of the important components of ASP initiatives with the intended aim of optimizing antimicrobial therapy while limiting toxicity and resistance [6]. The input of infectious disease (ID) specialists in the assessment of infection severity and the management of ATBs is important for both quality of care and cost containment [5].

Several previous studies and guidelines recommended switching from IV to oral antibiotics in hospitalized patients with several infectious diseases, including community-acquired pneumonia (CAP), acute pyelonephritis, skin and soft tissue infections (SSTIs), and intra-abdominal infections (IAI) [1, 6]. ES can shorten the duration of IV antibiotic therapy and LOS with no negative effect on patient outcome [7, 8]. In addition, significant cost saving from the use of early IV to oral ATB switch therapy (IVOST) or outpatient parenteral antibiotic therapy (OPAT) and discharge was demonstrated in previous studies [5, 9].

Many strategies and tools have been recommended to promote and optimize early ATB switching and early discharge for hospitalized patients, such as electronic reminders,
questionnaires, and checklists [10-13]. A possible pathway towards increasing the appropriateness of ATB use could be a formal reassessment of ATB therapy after 2-4 days when culture results allow for re-evaluation [7]. There are, however, a limited number of randomized controlled trials (RCTs) from low- and middle-income countries that have investigated the efficacy and efficiency of this ATB reassessment process.

Methods

Study setting and design

A cluster randomized controlled trial (RCT) was performed in general medical wards as cluster units at Siriraj Hospital (Bangkok, Thailand) during January 2019 to October 2019. Specialty units, such as the intensive care unit (ICU), cardiac care unit (CCU), respiratory care unit (RCU), or special unit for hematologic patients, were excluded. Each included ward has a capacity of 20 beds. This study aimed to evaluate the impact of infectious disease team review for the suitability of early IV to oral ATB switch therapy (IVOST), outpatient parenteral antibiotic therapy (OPAT), and early discharge using checklist criteria for patients receiving IV antibiotics (ATBs) versus control group. This trial was not registered elsewhere since the study does not involve a drug or device. Furthermore, the intervention in this study related less to included patients, and more to the acceptance (or not) of the ATB suggestion offered by the researchers to the treating physicians.

Study participants

Eligible patients were adults aged 18 years or older who were admitted to participating wards and who received IV ATBs for not more than 72 hours. We excluded patients who required a prolonged duration of IV antibiotic therapy, such as central nervous system (CNS) infection, infective endocarditis (IE), or vascular infection; neutropenic
patients; patients who discontinued ATB treatment within 24 hours; and, patients who refused to participate in the study.

Randomization and masking

The unit of randomization was general medical wards in the Department of Medicine. Participating wards were randomly allocated into 2 groups: intervention groups and control groups. The nature of the study design and intervention made masking of physicians and researchers impossible.

Control and intervention

Most of the antibiotics at Siriraj Hospital can be prescribed by any physician, except for restricted antibiotics that require ID approval before dispensing (preprescription authorization), such as colistin, linezolid, sitafloxacin, and tigecycline. Another group of antibiotics that are called controlled antibiotics, including piperacillin/tazobactam, meropenem, and imipenem, require ID review and authorization after 72 hours (postprescription review and authorization: PPRA). The responsible physician was required to complete the drug-use evaluation form for these controlled ATBs. In the present study, the intervention research team was composed of the ID team (one ID specialist and one ID fellow) and the clinical pharmacist team who work with the medical, nursing and healthcare team in each ward. All patients who received IV ATB for less than 72 hours according to the records kept by the ward pharmacist were approached for recruitment into this study. Patients determined to be eligible for recruitment by the ID team that were willing to participate were enrolled consecutively until we reached the target number of patients per cluster.

In the control wards, management of antibiotics (either converting IV to oral ATBs or OPAT) was left entirely to the judgment of the attending or primary physician. In the intervention wards, after obtaining written informed consent, the assessment was performed prospectively at enrollment (day 1 to day 3 of IV ATBs), day 5, and day 7 of ATB therapy.
using checklist criteria to define patient suitability for IV to oral ATB switching, OPAT, or discontinuation of ATB, as well as patient discharge. The types of drugs and doses of switched antibiotics were also recommended by the ID team. The checklist criteria and the suggestions for treatment or discharge were placed in the patient’s chart. In addition to placing the recommendation in the patient’s chart, the ID team also had a verbal discussion with the responsible primary physician team regarding the reasons behind the provided recommendation. However, the final decision to discontinue the antibiotic, switch to oral antibiotic or OPAT, or discharge as recommended by the ID team was left to the discretion of the treating physician.

The checklist criteria for suitability of ATB switching is shown in Table S1. Briefly, the infection was improving if there was a resolution of fever, decrease in white blood cell counts (WBC), ability to absorb and tolerate oral antibiotic, and the absence of any other major factor preventing discharge. When an attending physician did not switch a patient to oral antibiotics despite meeting all checklist criteria for doing so, he was asked to indicate the reason in a free text box on the checklist. Otherwise, there were no additional interventions by or formal consultations with the ID team.

**Outcome and data collection**

The primary outcomes were duration of IV antibiotics in the hospital and length of stay (LOS). The duration of IV antibiotics in the hospital was defined as the numbers of days that patients receives IV antibiotics for index infection, irrespective of the number of different drugs, until stopping antibiotics or changing to an oral form or OPAT. Antibiotic use was also quantified by days of therapy (DOT) and defined daily dose (DDD). DOT was measured by the sum of the number of days that a patient received each antibiotic for index infection, regardless of the dose. DDD was defined as the assumed average maintenance dose per day for a drug used for its main indication [14]. Secondary outcomes
were 30-day mortality, readmission rate within 30 days, recurrent infection rate at 14 days after the end of treatment, antibiotic cost, and total hospital cost during admission. The rate of reinfection and re-admission were retrieved from electronic medical record. Patients discharged before 30 days after enrollment were contacted by telephone to document their outcome at 30 days. Data collected included the demographic characteristics of patients; presumed site of infection; presence of sepsis, defined as Quick Sequential Organ Failure (qSOFA) score of 2 or more; microbiological results at enrollment, day 5 and day 7; and, information about the antibiotics selected, including the type, route of administration, susceptibility of antibiotic, modification of the antibiotic regimen occurring from enrollment to the end of therapy, planned duration of treatment, and acceptance rate with a suggestion from the ID team. The total duration of antibiotic therapy, including both intravenous and oral courses for index infection, was also obtained.

**Statistical analysis**

From 104 patients admitted to 3 medical wards during June 2018 in Siriraj Hospital, the mean duration of IV ATB in the hospital was 6.6 days, with a standard deviation (SD) of 5.30 days. The sample size was calculated based on the duration of IV antibiotics in the hospital. To detect 2 days shorter duration of IV antibiotics, and assuming a standard deviation of 5.30, 80% power, and a 5% significance level, the total sample size required under individual randomization was 224 patients. Assuming an intracluster correlation of 0.01 and 20% loss to follow-up with 8 clusters, a minimum of 46 patients per cluster was required for a total sample size of 368 patients or 184 patients per arm.

Descriptive statistics were used to characterize the sample data. Qualitative data were presented as frequency and percentage, while quantitative data were presented as median and range. Comparison of baseline demographics, clinical characteristics, and outcomes was performed between the control and intervention groups, and between those who survived and
those who did not survive. Mann-Whitney-U test was used to compare quantitative data, and Pearson’s chi-square, Yates’ continuity correction, or Fisher’s exact test was used to compare qualitative data, as appropriate. Subgroup analysis of sepsis, culture proven from any site or from blood and mortality was performed in a post hoc manner. Marginal logistic regression model using generalized estimating equations (GEE) was used to examine for association between factors and 30-day mortality. Statistical analysis was performed using PASW Statistics 18.0 (SPSS, Inc., Chicago, IL, USA) and Stata version 14 (StataCorp, College Station, TX, USA). All statistical tests were two-sided, with a \( p \)-value<0.05 indicating statistical significance.

**Results**

Among the 664 patients who were on IV antibiotic therapy, 296 patients were excluded. The reasons for exclusion are shown in Figure 1. A total of 368 patients who still required IV antibiotic therapy were included, with 184 patients in wards randomized to the intervention arm, and 184 patients in wards randomized to control. Baseline characteristics were similar in both groups (Table 1). Sepsis and septic shock were found in 46 (25%) and 25 cases (13.6%), respectively, and equally in both groups. Bacteremia was observed in 68 patients (18.5%).

**Antibiotic management and physician acceptance rate in the intervention ward**

After assessment within 72 hours of IV antibiotics, 13 cases (7%) had no indication to continue ATBs, and 13 cases (7%) met the criteria for IVOST or OPAT. By day 7 of IV antibiotics, only half of patients still required antibiotics. The overall physician acceptance rate with ID suggestions was 95.1%, 91.2%, and 91.5% on the day of enrollment, on D5, and on D7 of IV antibiotics, respectively (Table 2). However, acceptance of the suggestion from the ID team varied depending on the type of suggestion. Acceptance of a suggestion to stop
antibiotics or switch to oral ATBs was highest (89.2%) on day 7. The main reasons for not complying with antibiotic switching suggestions, which were available in 31 of 36 episodes, included team and hierarchical issues (17 of 31, 54.8%), such as non-agreement by the primary physician and believing that IV antibiotics are stronger than oral antibiotics (14 of 31, 45.2%). The three main causes of delayed hospital discharge were unresolved or additional care required for comorbidities, the need for time to prepare home support, and waiting for forthcoming medical or surgical procedures before discharge. The median turnaround time for culture results was 4 days (range: 2-8). Table S2 shows the types of pathogens by the site of infection, types of antibiotics, and the duration of treatment for index infection.

**Primary and secondary outcome**

Overall, ID team review using predefined checklist criteria for IVOST or OPAT did not reduce the duration of IV antibiotic therapy (7 days vs. 7 days, \( p=0.327 \)) or LOS (9 days vs. 10 days, \( p=0.951 \)) compared to the control group. The duration of total antibiotics, including IV and oral ATBs, for index infection was similar in both groups regardless of measurement method (Table 3). Post-hoc analysis of a subgroup of patients categorized by presence of sepsis, positive culture from any site, or positive culture from blood is shown in Table 4. Notably, patients without sepsis in the intervention group received a significantly shorter duration of IV antibiotics than in the control group when quantified by DOT (7 days vs. 8 days, \( p=0.027 \)) and DDD (7 days vs. 9 days, \( p=0.017 \)). Although patients without bacteremia in the intervention group tended to have a shorter duration of IV antibiotics (7 days vs. 9 days, \( p=0.273 \)), shorter DOT (8 days vs. 10 days, \( p=0.456 \)), and lower DDD (8.7 days vs. 9.1 days, \( p=0.815 \)) than in the control group, the differences between groups did not achieve statistical significance.
Factors associated with 30-day mortality

The mortality rate of patients in the intervention group was markedly lower than that in the control group (39 cases [21.7%] vs. 58 cases [32.2%], p=0.032). Eleven of 39 patients (28.2%) in the intervention group and 23 of 58 patients (39.6%) in the control group died within 7 days of enrollment. When excluding those who died within 7 days of enrollment, there were no significant differences in the duration of IV antibiotic therapy between groups. There was no difference in the 30-day readmission rate, total cost of ATBs, or total cost of admission (Table 3). Baseline characteristics compared between survivors and non-survivors are shown in Table S3. Almost all factors from univariate analysis, including age (adjusted odds ratio [aOR]; 1.1, 95% confidence interval [CI]: 1.0-1.1), hematologic malignancy (aOR: 3.9, 95% CI: 1.6-9.6), solid malignancy (aOR; 2.5, 95% CI: 1.2-4.9), and presence of sepsis (aOR: 2.9, 95% CI: 1.6-5.7) were independently associated with mortality in multivariable analysis. Alternatively, female gender (aOR: 0.7, 95% CI: 0.5-0.9), diabetes mellitus (aOR: 0.5, 95% CI: 0.3-0.9), and intervention (aOR: 0.5, 95% CI: 0.39-0.66) were shown to be protective factors against death.

Discussion

In the present study, ID team review for the suitability of IV-PO ATB switch therapy (IVOST) and early discharge using checklist criteria did not result in a shorter duration of IV antibiotics in the hospital or LOS despite the fact that one-fourth of patients in the intervention wards could discontinue all antibiotics within 7 days. We enrolled adult patients who had been receiving IV ATBs for not more than 72 hours. Therefore, the time of enrollment would be day 1 to day 3 of IV ATBs, and we assessed the patients’ condition on day 5, which is appropriate timing for reassessment of clinical and laboratory data. This result is in contrast to a previous meta-analysis that showed a reduction in the duration of antibiotic
treatment by 1.95 days from 11 days to 9.1 days, and reduced LOS by 1.12 days from 12.9 days to 11.8 days by using a number of stewardship interventions. Those interventions included either single or combined intervention, such as education on antibiotic use (enabling), review and feedback, or restrictive intervention [8]. However, the studies included in that meta-analysis were published over a 70-year period (1947-2015), and many studies in and recommendations for shorter duration of antibiotics have been published over time [15, 16]. In the present study, even in the control group, the median duration of IV antibiotics and LOS was 7 days and 10 days, respectively, which is shorter than the findings in the intervention group reported in the aforementioned meta-analysis. Another previous meta-analysis to determine the effectiveness of AMS interventions in low- and middle-income countries [10, 17] had no strong conclusion regarding the effectiveness of intervention due to the low quality of the study, risk of contamination, and publication bias.

The reasons why ID team review for the suitability of IVOST and early discharge using checklist criteria did not reduce the duration of IV ATBs might be due to several reasons. The first reason could be the delay in turnaround time (TAT) for culture results (4 days), which led to difficulty in making suggestions on oral ATBs or OPAT before getting the results of antimicrobial susceptibility testing. The TAT in a prior study conducted in high income countries using similar interventions was only 3 days, which is shorter than the TAT in our study [13]. Further studies are needed to determine whether a faster TAT of culture or advanced testing will be able to reduce the duration of IV antibiotic therapy in resource-limited settings. In addition, the switching criteria required not only clinical criteria, but also a decrease in WBC count of less than 12,000 cells/mm$^3$. However, we did not routinely check WBC. Lastly, although patients may have met the switching criteria, complex conditions of patients admitted in medical department, such as comorbidities, and issues of home support could prevent early discharge.
The rate of physician acceptance with ID team suggestions using the checklist criteria was higher than 90% in this study. This suggests that ID team review and suggestions did not adversely affect communication and trust among the care team, as mentioned in previous studies [8].

Notably, a significant decrease in the duration of IV antibiotics was observed in patients without sepsis in the intervention ward. A duration of antibiotic therapy of 7-10 days is generally adequate for sepsis patients, and longer courses are necessary only in some patients, such as those with slow clinical response or with undrainable foci [18]. A shorter duration of antibiotic therapy even in sepsis patients is safe without affecting treatment success [19]. Decisions on the duration of antibiotic should be considered depending on patient-related factors and the type of infection [20]. However, the subgroup of patients with sepsis was analyzed in a post hoc manner, so the results should be interpreted with caution until confirmed in future study.

From previous systematic review [8], interventions for improving antibiotic prescription for hospital inpatients were effective without adversely affecting mortality (11% in both arms). In our study, the patients in the intervention wards had 33% lower mortality than those in the control wards (39 cases [21.7%] vs. 58 cases [32.2%], p=0.032, respectively); however, there was no difference in the readmission rate, the cost of antibiotics, or the total cost of care between groups. Recruitment bias is an unlikely explanation for the mortality benefit because the patient characteristics were very similar between groups. Intervention was also shown to be a protective factor against mortality in multivariate analysis. This finding might be explained by early ID consultation, and that ID physicians are more likely to select the type and optimum duration of appropriate antibiotics for individual patients. However, we did not find any difference in the proportion of susceptible antibiotic therapy, duration of IV, or total antibiotics for index infection in our
Several previous studies reported mortality benefit of early ID consultation [21, 22]. Since there are no good explanations for the difference in mortality between groups, the possibility of false relationship may have existed.

The intervention in our study is partially similar to post-prescription review and feedback [23], but our intervention focused on evaluation of the patients’ condition to determine whether they were reaching a status according to the checklist criteria where they could be safely switched to oral antibiotic or outpatient parenteral antibiotic therapy (OPAT) or discharged. Although clinical judgement specific to making treatment recommendations was permitted in our study design, uncertainty and variation in clinical judgement in medicine exists in all forms. A technical document, such as a checklist, is developed based on the current literature and best practice. A checklist is a list of action items arranged in a logical and consistent manner; therefore, it allows the evaluator to record the presence or absence of the individual items listed. The checklist criteria are, therefore, not only useful as a mnemonic device, but also as a tool to achieve standardization of process, and it enhances the objectivity and reproducibility of an assessment.

A key strength of the present study is the study design with cluster RCT, which could minimize contamination of the intervention as compared to a traditional RCT design. Our study design may also have increased physician acceptance with ID team suggestions since the intervention was implemented at the ward level. In addition, the patients in our study had a variety of conditions compared to prior studies that focused on a specific infection, pathogen, or population. The limitations of our study include the limited generalizability of our findings to other hospital settings, since our center is a national referral center that is commonly referred more complicated cases, with multiple comorbidities, and with more risk of acquisition of or infection with multidrug-resistant (MDR) pathogen. Therefore, the checklist criteria for IVOST or OPAT and discharge criteria may not be applied in different
settings or hospitals, such as in the surgical department, pediatric patients, or in rural hospitals.

In conclusion, ID team review using checklist criteria did not result in a shorter duration of IV antibiotic or LOS in overall patients. However and notably, the duration of IV antibiotic therapy in the intervention group was significantly reduced among non-sepsis patients. Further studies are needed to determine whether a faster turnaround time of culture or advanced testing will be able to reduce the duration of IV antibiotic therapy.
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Conflict of interest statement

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

Patient consent statement

The study protocol was approved by the Siriraj Institutional Review Board (COA numbers Si 030/2019), and written consent was obtained from patients.

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Table 1: Baseline demographic and clinical characteristics compared between the control and intervention groups (N=368)

| Characteristics                | Control (n=184) | Intervention (n=184) | p-value |
|--------------------------------|----------------|----------------------|---------|
| Age (years), median (range)    | 70 (18-101)    | 68 (18-93)           | 0.383   |
| Male gender, n (%)             | 92 (50.0%)     | 92 (50.0%)           | 1.000   |
| ID attending, n (%)            | 14 (7.6%)      | 12 (6.5%)            | 0.839   |
| ID consultation, n (%)         | 27 (14.7%)     | 22 (12.0%)           | 0.361   |
| Underlying disease, n (%)      | 159 (86.4%)    | 172 (93.5%)          | 0.024   |
| HT                             | 107 (58.2%)    | 98 (53.3%)           | 0.401   |
| Dyslipidemia                   | 74 (57.8%)     | 54 (42.2%)           | 0.038   |
| DM                             | 63 (34.2%)     | 67 (36.4%)           | 0.744   |
| CKD                            | 45 (24.5%)     | 50 (27.2%)           | 0.634   |
| Solid malignancy               | 22 (12.0%)     | 37 (20.2%)           | 0.044   |
| Hematologic malignancy         | 13 (7.1%)      | 10 (5.4%)            | 0.667   |
| Autoimmune disease             | 12 (6.5%)      | 17 (9.2%)            | 0.568   |
| Steroid use                    | 10 (5.4%)      | 12 (6.5%)            | 0.826   |
| Chronic Liver disease          | 10 (5.4%)      | 14 (7.6%)            | 0.526   |
| HBV or HCV infection           | 9 (4.9%)       | 14 (7.6%)            | 0.389   |
| Chronic lung disease           | 8 (4.3%)       | 24 (13%)             | 0.006   |
| Old TB                         | 8 (4.3%)       | 10 (5.4%)            | 0.629   |
| HIV infection                  | 6 (3.3%)       | 2 (1.1%)             | 0.284   |
| Condition               | Number (Percentage) | Number (Percentage) | p-value |
|-------------------------|---------------------|---------------------|---------|
| Sepsis, n (%)           | 46 (25.0%)          | 46 (25.0%)          | 1.000   |
| Septic shock, n (%)     | 25 (13.6%)          | 25 (13.6%)          | 1.000   |
| Site of infection, n (%)|                     |                     |         |
| Pneumonia               | 76 (41.3%)          | 86 (46.7%)          | 0.345   |
| UTI                     | 31 (16.8%)          | 35 (19.0%)          | 0.684   |
| IAI                     | 30 (16.3%)          | 29 (15.8%)          | 1.000   |
| Primary bacteremia      | 13 (7.1%)           | 13 (7.1%)           | 1.000   |
| SSTI                    | 12 (6.5%)           | 6 (3.3%)            | 0.227   |
| Others                  | 22 (12%)            | 15 (8.2%)           | 0.298   |
| Any culture positive, n | 63 (34.4%)          | 72 (39.6%)          | 0.364   |
| Received susceptible ATB, n (%) | 53 (84.1%) | 59 (81.9%) | 0.915 |
| Positive blood culture, n (%) | 33 (17.9%) | 35 (19.0%) | 0.673 |

A p-value <0.05 indicates statistical significance.

ID attending was defined as the attending physician who acted as the primary physician, and also is a specialist in infectious diseases.

ID consultation was defined as the patients who had a formal ID consultation from primary physician.

**Abbreviations**: ID, infectious diseases; HT, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; HBV, hepatitis B; HCV, hepatitis C; TB, tuberculosis; HIV, human immunodeficiency virus; UTI, urinary tract infection; IAI, intra-abdominal infection; SSTI, skin and soft tissue infection.
Table 2: Summary of ID suggestions on antibiotic management and physician acceptance in the intervention ward

| ID suggestion | Stop | Oral ATB | OPAT | Continue IV | Discharge |
|---------------|------|----------|------|-------------|-----------|
| **Day (D) of ATB** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| D2-3 (n=184) | 13/184 | 11/184 | 2/184 | 158/184 | 3/184 |
| | (7.0%) | (6.0%) | (1.1%) | (85.9%) | (1.6%) |
| Accept (n=175) | 9/13 | 8/11 | 0/2 | 158/158 | 3/3 |
| | (69.2%) | (72.7%) | (0%) | (100.0%) | (100.0%) |
| D5 (n=170) | 26/170 | 36/170 | 6/170 | 102/170 | 23/170 |
| | (15.3%) | (21.2%) | (3.5%) | (60.0%)* | (13.5%) |
| Accept (n=155) | 22/26 | 28/36 | 5/6 | 100/102 | 20/23 |
| | (84.6%) | (77.8%) | (83.3%) | (98.0%) | (86.9%) |
| D7 (n=141) | 37/141 | 24/141 | 6/141 | 74/141 | 18/141 |
| | (26.2%) | (17.0%) | (4.3%) | (52.5%)* | (12.8%) |
| Accept (n=129) | 33/37 | 19/24 | 3/6 | 74/74 | 11/18 |
| | (89.2%) | (79.2%) | (50.0%) | (100.0%) | (61.1%) |

*Suggested escalating antibiotic for 5 cases on D5 (comply 100%), and 4 cases on D7 (comply 100%)

**Abbreviations:** ID, infectious disease; ATBs, antibiotics; OPAT, outpatient antibiotic therapy; IV, intravenous
Table 3: Primary and secondary study outcomes compared between the control and intervention groups (N=368)

| Outcomes                           | Control       | Intervention  | p-value |
|-----------------------------------|---------------|---------------|---------|
|                                   | (n=184)       | (n=184)       |         |
| **Primary outcome**               |               |               |         |
| IV ATB for index infection        |               |               |         |
| Duration of IV ATB, days          | 7 (2-30)      | 7 (2-35)      | 0.327   |
| Days of IV ATB, days              | 8 (2-68)      | 7.5 (2-62)    | 0.205   |
| DDD of IV ATB                     | 9 (0.8-98)    | 8 (1.2-51)    | 0.534   |
| Total ATB for index infection     |               |               |         |
| Duration of IV ATB, days          | 8 (2-34)      | 8 (2-35)      | 0.784   |
| Days of IV ATB, days              | 11 (2-68)     | 11 (2-62)     | 0.292   |
| DDD of IV ATB                     | 11 (0.7-200)  | 11 (1.2-88.3) | 0.534   |
| Length of stay, days              | 9 (1-92)      | 10 (1-104)    | 0.951   |
| **Secondary outcome**             |               |               |         |
| 30-day mortality, n (%)           | 58 (32.2%)    | 39 (21.7%)    | 0.032   |
| 30-day readmission rate, n (%)    | 25 (13.8%)    | 30 (16.5%)    | 0.573   |
| Recurrent infection*, n (%)       | 26 (14.1%)    | 20 (10.9%)    | 0.344   |
| Same infection site, n (%)        | 14 (53.8%)    | 9 (45%)       | 0.463   |
| Total ATB cost, baht              | 3,024         | 2,879         | 0.621   |
Quantitative data are reported as median (min, max) unless stated otherwise.

A p-value <0.05 indicates statistical significance

**Abbreviations:** IV, intravenous; ATB, antibiotic; DDD, defined daily dose; LOS, length of stay

*Recurrent infection was defined as reemergence of infection at 14 days after end of treatment*
Table 4: Study outcomes categorized by presence of sepsis, and culture results compared between the control and intervention groups (N=368)

| Study outcomes | Control  | Intervention  | p-value |
|----------------|----------|---------------|---------|
| (n=184)        | (n=184)  |               |         |
| Duration of IV ATB, days |          |               |         |
| Presence of sepsis |          |               |         |
| Yes (n=92)      | 7 (2-30) | 8.5 (3-30)    | 0.329   |
| No (n=276)      | 7 (2-30) | 7 (2-35)      | 0.076   |
| Culture-proven |          |               |         |
| Yes (n=135)     | 9 (4-30) | 8 (3-32)      | 0.085   |
| No (n=230)      | 7 (2-30) | 7 (2-35)      | 0.745   |
| Positive culture |        |               |         |
| Blood (n=68)    | 10 (4-30)| 10 (3-32)     | 0.198   |
| Non-blood (n=67)| 9 (4-30)| 7 (3-21)      | 0.273   |
| Days of IV ATB, days |          |               |         |
| Presence of sepsis |          |               |         |
| Yes (n=92)      | 9 (2-54) | 11 (2-62)     | 0.284   |
| No (n=276)      | 8 (2-68) | 7 (2-44)      | 0.027   |
| Culture-proven |          |               |         |
| Yes (n=135)     | 11 (4-68)| 9.5 (3-43)    | 0.135   |
| No (n=230)      | 7 (2-59) | 7 (2-62)      | 0.460   |
| Positive culture |        |               |         |
| Blood (n=68)    | 12 (4-54)| 12 (3-42)     | 0.237   |
| Non-blood (n=67)| 10 (4-68)| 8 (3-43)      | 0.456   |
### DDD of IV ATB

#### Presence of sepsis

|        | Median (Min, Max) | IQR (Min, Max) | P-value |
|--------|------------------|----------------|---------|
| Yes (n=92) | 8.5 (2-89.75)   | 11.6 (2.3-51)  | 0.144   |
| No (n=276)  | 9 (0.8-98)      | 7 (1.16-51)    | **0.017** |

#### Culture-proven

|        | Median (Min, Max) | IQR (Min, Max) | P-value |
|--------|------------------|----------------|---------|
| Yes (n=135) | 10.7 (0.8-98)   | 9.7 (3-47)     | 0.253   |
| No (n=230)  | 7.8 (1.5-47)    | 7.1 (1.2-51)   | 0.266   |

#### Positive culture

|        | Median (Min, Max) | IQR (Min, Max) | P-value |
|--------|------------------|----------------|---------|
| Blood (n=68) | 14 (2.8-89.7)   | 10 (3-28.5)    | 0.086   |
| Non-blood (n=67) | 9.1 (0.8-98) | 8.7 (3-47)     | 0.815   |

Quantitative data are reported as median (min, max) unless stated otherwise.

A p-value <0.05 indicates statistical significance.

**Abbreviations:** IV, intravenous; ATB, antibiotic; DDD, defined daily dose; LOS, length of stay
Figure legend

**Figure 1**: CONSORT flow diagram showing patient enrollment and flow through the study
Figure 1

Assessed for eligibility (15 wards)

Excluded: 7 specialty wards
- ICU (2), CCU (1), RCU (1), BMT (1)
- Hematology wards (2)

Randomization (8 wards)

Allocated to intervention (4 wards)
Assessed for eligibility (350 patients)
Met exclusion criteria (166 patients)
- Need prolonged IV ATB or receiving IV ATB more than 72 hours (127)
- Neutropenia (13)
- Before enrollment
  - Dead (15)
  - Off ATB (2)
  - Discharge (2)
  - Refer (1)
  - Others (6)

Received intervention 184 participants
(46 patients per ward)

Analyzed 4 wards, 46 patients/ward
184 participants
Excluded from analysis: 0

Allocated to control (4 wards)
Assessed for eligibility (314 patients)
Met exclusion criteria (130 patients)
- Need prolonged IV ATB or receiving IV ATB more than 72 hours (102)
- Neutropenia (15)
- Before enrollment
  - Dead (7)
  - Off ATB (3)
  - Discharge (1)
  - Others (2)

Received usual care 184 participants
(46 patients per ward)

Analyzed 4 wards, 46 patients/ward
184 participants
Excluded from analysis: 0