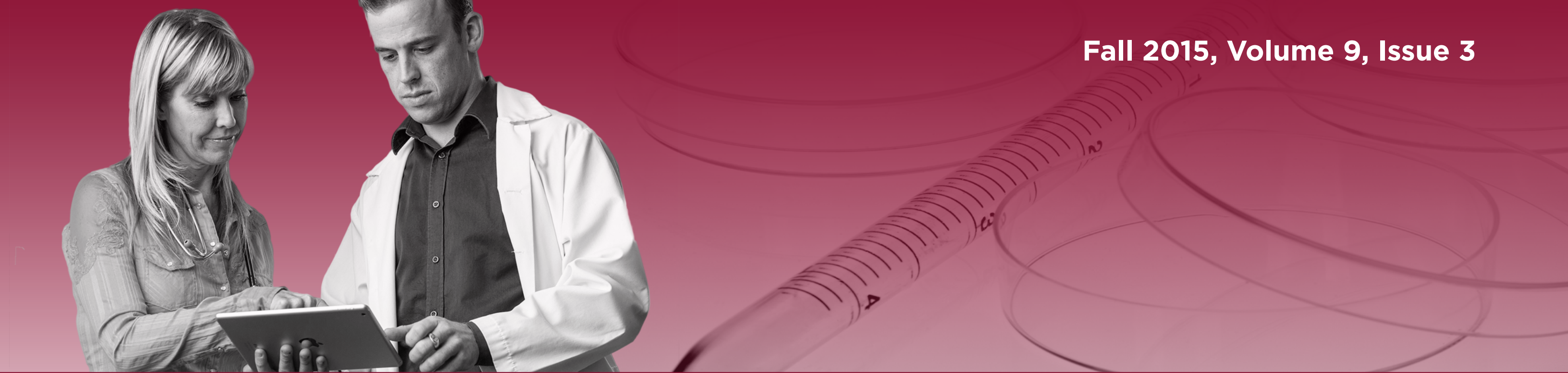


Fall 2015, Volume 9, Issue 3

the Translator

Canadian Pharmacy ➤ Research ➤ Health Policy ➤ Practice ➤ Better Health

The Pharmacists Role in Antimicrobial Resistance

Antimicrobial resistance (AMR) poses a significant threat to the wellbeing of society. The issue comes at a time when there is a limited number of new antibacterial agents being developed, the use of antibiotics in livestock is being questioned and greater awareness is placed on the value of immunization in mitigating the spread of infectious disease.

Fédération Internationale de Pharmacie (FIP) recently stated that pharmacists have a key role to play in implementing the World Health Organization's (WHO) Global Action Plan to tackle AMR. Pharmacists in general are playing an increasingly important role in triage. In the case of AMR this is particularly important to help restrict the use of antibacterial medications to situations in which there is a valid need and to ensure that patients use their antibacterial medications appropriately.

In this issue of *the Translator*, we identify a number of novel examples of pharmacy programs aimed at addressing antimicrobial resistance:

- The Impact of Pharmacists on Antimicrobial Stewardship Teams in a Community Setting
- Pharmacists Improve Patient Outcomes after Emergency Department Discharge
- Pharmacists Play a Key Role in Educational Interventions
- Pharmacist Led Antimicrobial Therapy Significantly Decreases Duration of IV Treatment

Impact of Pharmacists on Antimicrobial Stewardship Teams in a Community Setting.

Box MJ, Sullivan EL, Ortwine KN, et al. Outcomes of rapid identification for gram-positive bacteremia in combination with antibiotic stewardship at a community-based hospital system. Pharmacotherapy 2015 Mar;35(3):269-76. doi: 10.1002/phar.1557.

Corresponding author: Kristina F. Goerke, MBA, CLS, MT (ASCP), goerke.kristina@scrippshealth.org

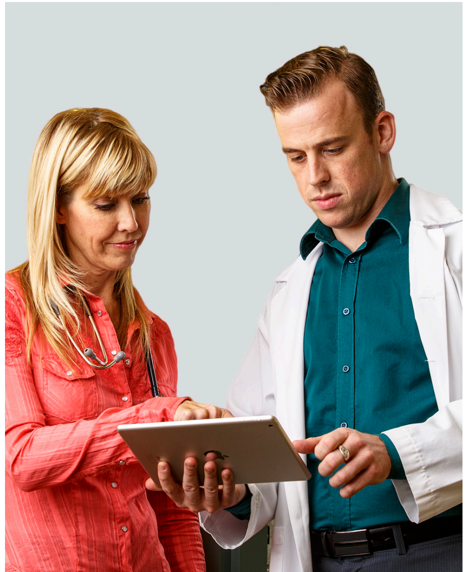
Issue: Choosing the correct antibiotic therapy for a condition in a timely manner is a main point of focus in treating bloodstream infections.[1] Rapid identification of pathogens is essential and can help pharmacists optimize antimicrobial regimens sooner than traditional methods,[2] leading to decreased antibiotic use, length of hospital and intensive care stay, and mortality. In addition to pathogen identification, a dedicated Antibiotic Stewardship Team (AST) providing prompt notification of results and facilitating

The Translator is an initiative by the Canadian Pharmacists Association to support the knowledge translation between pharmacy practice research and health policy. Each issue selects a number of pharmacy practice research articles, briefly summarizes them and discusses the health care policy implications. These articles are submitted by researchers who have a strong desire to support evidence-based health care policy and best practices.

Canadian Pharmacists Association
Association des Pharmaciens du Canada

timely interventions is essential to achieving improved clinical outcomes. Unfortunately, most of the studies looking at rapid identifications have been set in tertiary academic medical centres.[3-4] Implementing rapid testing in a community hospital setting requires more study, as community hospitals often lack antibiotic stewardship programs and pharmacists trained in infectious diseases, and have limited microbiology resources.

Solution: A multicentre, pre-post, quasi-experimental study was conducted at five acute care centres in San Diego, California, to measure the combined effect of rapid identification and a physician/pharmacist AST, compared to traditional care. Because each hospital did not have an infectious disease pharmacist present seven days a week, the clinical pharmacists at each site were trained to interpret the blood culture results and determine the antibiotic treatment of choice. The Verigene Gram-Positive Blood Culture (BC-GP) test was used for rapid identification, and could also be used to detect resistance to vancomycin and methicillin. Of the 312 patients with gram-positive bacteraemia who were screened, 103 were included in the pre-intervention group and 64 included in the post-intervention group. The pre-intervention group consisted of patients who visited the hospital in 2011 and received traditional treatment. Patients in the post-intervention group visited the hospital in 2014 and received additional Verigene BC-GP/AST management. In the traditional group, positive blood cultures were Gram stained on site, organisms were identified and reported to the nursing staff, who contacted the physician with the results.



Pharmacists can be utilized to successfully implement rapid diagnostics with antimicrobial stewardship programs.

In the intervention group, Verigene BC-GP testing was performed post-Gram stain, and the results were communicated to a clinical pharmacist, who collaborated with the physician to make the proper recommendations for antibiotic therapy. If the Verigene BC-GP would not provide additional information, it was not performed, but the pharmacist intervention was still implemented.

It was found that rapid identification with AST intervention significantly improved the mean time to targeted antibiotic therapy (61.1 vs. 35.4 hrs, $p<0.001$). More specifically, time to targeted therapy was improved for methicillin-sensitive *Staphylococcus aureus* (MSSA) (63.4 vs. 36.7 hrs, $p<0.01$), *Enterococcus faecalis* (68.54 vs. 20.13 hrs, $p<0.01$), and *Streptococcus* strains (52.4, vs. 36.3 hrs, $p=0.01$). In addition, the mean duration of antibiotic therapy for blood cultures considered to be a contaminant decreased in the intervention group (42.3 vs. 24.5 hrs, $p=0.03$). Rapid identification combined with AST management were associated with a lower median length of stay (9.1 vs. 7.2 days, $p=0.04$) and similar mortality rates (9.1% vs. 9.2%, $p=0.98$). Of the 64 patients in the intervention group, 25 interventions (39%) were made by an infectious disease pharmacists and 39 (61%) were by a clinical pharmacist; 54 interventions (84%) were accepted by the physician. Acceptance rates were similar for the infectious diseases pharmacists and clinical pharmacists.

Implications: Rapid diagnostics for gram-positive bacteraemia with AST intervention is associated with improved clinical outcomes. These outcomes can be realistically achieved in a community hospital, in which there may be a shortage or a lack of resources. The overall goal of antibiotic stewardship is to maximize patient outcomes while minimizing the unintended consequences of antibiotic use. This study suggests that pharmacists can be utilized to successfully implement rapid diagnostics with antimicrobial stewardship programs. In addition, a rapid diagnostic workflow in a community-based health care system can also improve antimicrobial utilization and reduce costs.

Background and Methods: Patients were excluded from the study if they had a mixed bloodstream infection, were under hospice or palliative car, were on antibiotic treatment for a concomitant infection unrelated to the positive blood culture, had a culture result that was known at the time of admission, did not receive antibiotic therapy (suspecting a contaminant) or were an oncology or transplant patient. No significant differences were found between the pre- and post-intervention groups in respect age, gender, antibiotic allergy, prevalence of comorbid conditions, presence of an infectious disease (ID) consult, or intensive care unit (ICU) stay. Regarding the notification of the result to the physicians, the times were restricted to between 7 a.m. and 7 p.m., as it was felt that cross-covering physicians would be hesitant to deescalate or discontinue antibiotics with patients for whom they were not directly involved in their care. The year 2011 was chosen for the pre-intervention group because antibiotic stewardship programs were not well established at all five acute care centres at this time. Measures with continuous outcomes were analyzed using at student t test or Wilcoxon rank-sum test for non-normally distributed data. Dichotomous data were analyzed by the Pearson chi-squared test or Fisher exact test. One of the limitations of this study was the small sample size, and the retrospective non-randomized data collection.

1. Frye AM, Baker CA, Rustvold DL. Clinical impact of a real-time PCR assay for rapid identification of Staphylococcal bacteremia. *J Clin Microbiol* 2012.
2. Bauer KA, Perez KK, Forrest GN. Review of rapid diagnostic tests used by antimicrobial stewardship programs. *Clin Infect Dis* 2014.
3. Huang AM, Newton D, Kunapuli A. Impact of organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. *Clin Infect Dis* 2013.
4. Perez KK, Olsen RJ, Musick WL. Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs. *Arch Pathol Lab Med* 2013.

Pharmacists Improve Patient Outcomes after Emergency Department Discharge

Baker SN, Acquisto NM, Dodds Ashley E, Fairbanks RJ, Beamish SE, Haas CE. Pharmacist-managed antimicrobial stewardship program for patients discharged from the emergency department. *J Pharm Pract* 2012 Apr;25(2):190-4. doi: 10.1177/0897190011420160. Epub 2011 Nov 17.
Corresponding Author: Nicole M. Acquisto, PharmD, BCPS, nicole_acquisto@urmc.rochester.edu

Issue: Multi-drug resistant pathogens are a growing concern when treating nosocomial and community-associated infections. They are associated with increased morbidity, mortality and costs.[1] Antimicrobial stewardship programs are one method that can be used to control the rise in resistance and improve the quality of patient care. Inappropriate empiric antibiotic therapy may lead to hospital readmission and complications for the patient, secondary to infection.

Antimicrobial agents are commonly prescribed to patients who are discharged from the emergency department (ED). However, there is often limited or inconsistent follow-up of culture results to systematically ensure appropriate therapy.[2-3] A wide variety of services can be provided by pharmacists in this practice setting, including providing essential patient care and education, managing medication services, providing education or information to other health care professionals, contributing to quality improvement initiatives and participating in research. Research has shown that pharmacists play an important role in the ED, but there is a need for data supporting this in specific patient outcomes, since the majority of the literature addresses adverse drug event prevention and cost-containment.[4-6]

Solution: There is already a growing pharmacy presence in ED settings; therefore, a logical expansion of services provided by the emergency medicine (EM) clinical pharmacist is antimicrobial stewardship. To measure the effects of an EM clinical pharmacist-managed antimicrobial stewardship program, 212 patients at the University of Rochester Medical Centre with positive cultures were split into a pre-implementation group (n=132) and a post-implementation group (n=80). In the pre-implementation group screening of culture reports and follow-up was done by nurse practitioners and physician assistants. In the post-implementation group, an EM clinical pharmacist assumed the responsibilities of reviewing culture results and follow-up, as well as providing educational seminars to providers regarding appropriate empiric antimicrobial selection. The primary outcomes measured were time until positive culture review and time to physician or patient notification, whereas the secondary outcome was appropriateness of therapy in an empiric sense.

EM clinical pharmacist-managed program decreases time to appropriate therapy.

The median time to positive culture review following collection in the pre-implementation group was 3 days (range 1–15) compared to 2 days (range 0–4) in the post-implementation group (p=0.0001). Not all patients with positive cultures required physician or patient notification due to appropriate empiric treatment given in the ED or cultures that were deemed contaminated by the EM clinical pharmacist. The median time to patient or primary care provider (PCP) notification was 3 days (range 1–9) for pre-implementation group compared to 2 days (range 0–4) for the post-implementation (p=0.01). Empiric antimicrobial therapy was appropriate for 88.9% of the cultures in the pre-implementation group and for 87% of the cultures in the post-implementation group (p=0.75). Final antimicrobial therapy was appropriate for 95.7% of the cultures in the pre-implementation group and for 100% of the cultures in the post-implementation group (p=0.1). Patients were only included in the final antimicrobial therapy assessment if their therapy was not changed (e.g., patient remained on same antibiotic that was started) or if changes to their antimicrobial regimen were known.

Implications: An EM clinical pharmacist-managed program significantly decreases both time to positive culture review and time to patient or physician notification when indicated. Although the study was not able to evaluate the clinical outcomes associated with decreased time to appropriate therapy, there are a variety of studies for in-patient settings that show an improved time to appropriate antibiotic therapy leads to better patient outcomes. One of the limitations with the study was that the EM clinical pharmacist at the institution was available Monday through Friday from 1100 to 1900, but the mid-level providers were still responsible for culture follow-up on the weekends. This is reflected in the time dependent endpoints in the post-implementation group where the range was reported up to 4 days, meaning that the effect of the pharmacist may be larger than reported (since the publication of this study, the EM clinical pharmacist group has expanded allowing the ED antimicrobial stewardship program to be covered by the pharmacist team 7 days a week).

Background and Methods: The time of year for both patient groups was kept the same to account for seasonal variation in infectious processes. Time to positive culture review was defined as the time from patient presentation to the ED, using the documented triage time to the first time the culture was reviewed. Antimicrobial therapy was deemed inappropriate if the antibiotic prescribed would not treat the presumed/documented pathogen based on the reported spectrum of activity, the recommendation was inconsistent with the IDSA or local guidelines for the patient's infection, or local data implied the initial therapy was inappropriate (institution-specific antibiogram). The primary endpoints were analyzed using the Wilcoxon Rank Sum Test, while the secondary endpoints of appropriateness of therapy as empiric and definitive were presented as categorical data and compared using the Chi-square analysis or Fisher's exact test where appropriate.

1. Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *CID.* 2007;44:159–177.
2. Kumar A, Roberts D, Wood K, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589–1596.
3. Garey KW. Timing of fluconazole therapy and mortality in patients with candidemia. *Clin Infect Dis* 2006;43:25–31.
4. Elenbaas RM, Waeckerle JF, McNabney WK. The clinical pharmacist in emergency medicine. *Am J Hosp Pharm* 1977;34:843–846.
5. Fairbanks RJ, Hays DP, Webster DF, et al. Clinical pharmacy services in an emergency department. *Am J Health-Syst Pharm* 2004;61:934–937.
6. Kelly S, Hays D, O'Brien T, et al. Pharmacist participation in trauma resuscitation. The 40th Annual American Society of Health-System Pharmacists Midyear Clinical Meeting 2005; Rochester, NY: University of Rochester Medical Center, Strong Health; abstract.

Pharmacists Play a Key Role in Educational Interventions.

Muñoz EB, Dorado MF, Guerrero JE, Martínez FM. The effect of an educational intervention to improve patient antibiotic adherence during dispensing in a community pharmacy. Aten Primaria 2014 Aug-Sep;46(7):367-75. doi: 10.1016/j.aprim.2013.12.003. *Epub* 2014 Feb 26.
Corresponding author: Macarena Flores Dorado, maktub77@hotmail.com

Issue: Lack of treatment adherence and self-medication are two of the biggest problems in antibiotic misuse among patients.[1-3] Unlike drugs that only affect individual patients, misused antibiotics add to the global risk of bacterial resistance, which jeopardizes their effectiveness and can lead to overall increased morbidity, mortality, health demands, hospitalization, medical expense and impairment of the effectiveness of treatment for future patients.[4] Adherence has been specifically studied in chronic disease but there is a lack of studies focusing on acute disease such as infectious diseases. Education and knowledge is a key aspect in addressing the misuse of antibiotics and community pharmacists are in an ideal position to provide it.

Solution: A community pharmacy in Spain performed an open-label controlled trial which looked at the effect a pharmacist oral educational intervention had on patient antibiotic adherence. Patients were randomized to either the intervention group or the control group. Patients in the intervention group (IG) were educated according to a dispensing guideline drawn up by the head pharmacist. The intervention focused on providing individualized verbal information to the patient about treatment characteristics, duration, dosage regime and how to use the antibiotic. The intervention took place in a private area and lasted about 20 minutes. If the antibiotic was being dispensed for the first time, the pharmacist checked if there were criteria for not dispensing it (clinically relevant interaction or contra-indications, in which case the patient was referred to the physician), and if the patient understood the process of using the antibiotic through a knowledge test. If it was not the first time, treatment effectiveness was assessed, checking whether the antibiotic was being used correctly and safely through the same knowledge test. In all cases if a lack of knowledge was detected personalized information was provided. In the control group (CG), any questions asked by the patient were answered and the antibiotic was not dispensed if there were any criteria for not doing so, but no further action was taken. To determine the effectiveness of the intervention a telephone interview was carried out seven days after the dispensation. In the case of longer duration treatments, the call was delayed until the end date of the treatment.

Pharmacists educating patients on antibiotic therapy helps improve clinical outcomes.

Of the 126 patients included, 62 were in the CG and 64 were in the IG. Adherence to the antibiotic treatment was 48.4% (CI: 36.4-60.6) in the CG and 67.2% (CI: 55.0-77.4) in the IG, with a difference of 18.8% (95% CI = 15.8-34.6; p = 0.033). Moderate noncompliance (more than one dose intake missing) was observed in 81.2% of patients in the CG and 38.1% in the IG, which had difference of 43.1% (95% CI = 16.4-63.1%; p = 0.001). There was no significant difference in the health perception, although it was found to be higher in the IG, with reports of being totally cured in 54.7% (95% CI = 42.6-66.3) of the IG and in 46.8% (95% CI = 34.9-59.0) of the CG (p = 0.297). Variables that positively influenced adherence were the knowledge of the antibiotic treatment before the intervention, and if the amount of medication dispensed was equal to the amount needed to complete the duration of treatment indicated by the physician.

Implications: The results suggest that knowledge is an important factor associated with medication adherence and that an intervention aimed at educating the patient may improve clinical outcomes associated with adherence. This study reinforces the pharmacists' role in improving the health care system through patient education in the rational use of medicines. However, since this was only conducted in one centre, it is necessary to conduct multicentre studies to support and verify that the implementation of these services in the pharmacy is, not only effective, but also feasible.

Methods and background: Sociodemographic and clinical variables were registered for all patients, and it was found that there were no statistically significant differences between the two groups. Adherence was evaluated by a combination of the Morisky-Green test and a self-reported pill count. Patients were considered compliant if they were categorized as such in both evaluations and non-compliant if they were found to be non-compliant in either of the two tests. Patients who took the liquid dosage forms were only evaluated using the Morisky-Green test. Non-treatment compliant patients were categorized as mild if a single dose was missed and moderate if more than one dose was missed. To assess potential factors associated with treatment adherence, a binary logistic regression model was drawn up using the backward stepwise method. Subject perceived health was evaluated by the question: "How did you get on with the treatment?" The answers were classified as cured, improved, the same or worse. One of the limitations of the study was that it used different indirect tests, which tend to overestimate adherence, although the use of two difference methods can reduce bias. In addition, the study was done in a local setting, which means the results cannot be extrapolated to wider settings.

1. Baos V, Barbero A, Diogene E, et al. Documento de consenso sobre el uso de antibióticos en atención primaria. *Aten Primaria* 2006;38:174-7.
2. Grigoryan L, Haaijer-Rysjamp FM, Burgerhof JG, et al. Self-medication with antimicrobial drugs in Europe. *Emerg Infect Dis* 2006;12: 452-9.
3. Sorensen SV, Baker T, Fleurence R, et al. Cost and clinical consequence of antibiotic non-adherence in acute exacerbations of chronic bronchitis. *Int J Tuberc Lung Dis* 2009;13:945-54.
4. Shehan B, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associate adverse events. *Clin Infec Dis* 2008;47:744-6.

Pharmacist Led Antimicrobial Therapy Significantly Decreases Duration of IV Treatment

Dunn K, O'Reilly A, Silke B, Rogers T, Bergin C. Implementing a pharmacist led sequential antimicrobial therapy strategy: a controlled before and after study. *Int J Clin Pharm* 2011 Apr;33(2):208-14. doi: 10.1007/s11096-010-9475-9. *Epub* 2011 Jan 25.

Corresponding author: Katherine Dunn, katedunn45@yahoo.co.uk

Issue: Sequential antimicrobial therapy, or switch therapy, is defined as the transition from intravenous (IV) to oral (PO) antimicrobial treatment. Sequential therapy is an important area of antimicrobial stewardship. Where appropriate, the earliest possible switch to PO therapy is promoted because IV treatment is more expensive, can have significant adverse effects such as catheter-related bloodstream infections, and is not always more efficacious.[1] Additionally, nursing time spent preparing IV doses is reduced and patient comfort and mobility is improved. Initiatives to promote sequential therapy have also been shown to reduce the duration of IV treatment and hospital stay with resulting cost savings.[2] Several studies have shown successful implementation of a sequential therapy strategy in medical patients requiring IV antimicrobials, with reductions in expenditure and length of hospital stay. However, a major limitation has been the uncontrolled design of these studies. Without a control group, it is impossible to determine whether observed differences before and after the intervention would have occurred regardless.

Solution: With their training and skills pharmacists are core members of antimicrobial stewardship teams and play a key role in improving antimicrobial use. Due to their extensive background in pharmacodynamics and pharmacokinetics, they are ideal for monitoring the switch from IV to PO antimicrobials. A controlled before and after study was done at a 753-bed academic hospital in Ireland. All adult patients admitted via the emergency department for at least 72 hours under the care of a single medical consultant were screened for inclusion. Those patients who were prescribed an IV antimicrobial during the first four days of admission were enrolled in the study. A guideline for IV to PO antimicrobial therapy transfer was developed by the antimicrobial stewardship committee. The study was split into phase 1 (before guideline implementation) and phase 2 (after guideline implementation) with a control and intervention group in both phases to eliminate bias. In phase 2 of the intervention group, patients on IV antimicrobial therapy had their drug charts highlighted. Study participants were then monitored by clinical pharmacists who applied the newly developed guidelines to their drug charts and contacted junior doctors when necessary to make a switch.

In the control group, the conventional practice of pharmacists reviewing the drug charts and contracting the prescribers to discuss an IV to oral switch was the same in phase 1 and phase 2. Study participants were then monitored by clinical pharmacists who applied the guidelines to their drug charts and made the switch when necessary.

A total of 236 patients were included in the study, 120 in the pre-implementation group and 116 in the post-implementation group. Across all groups, co-amoxiclav was the most commonly prescribed antimicrobial (42.1%), followed by piperacillin-tazobactam (12.7%), flucloxacillin (9.5%), benzylpenicillin (8.9%) and ciprofloxacin (7.9%). In the first phase, no significant difference was found in the duration of IV treatment between the control and intervention groups (P = 0.599). However, a significant difference was found between the control and intervention groups in the second phase (P = 0.02), with a reduced duration of IV treatment in the intervention group. Antimicrobials were switched in a more timely fashion in the intervention group compared to the control group in the second phase (P = 0.017). In the first phase, no significant difference was found. A total of 14 patients across all groups (5.9%) required reinstatement of IV therapy, following a switch to PO therapy or diagnosis of a new hospital-acquired infection. A small percentage of IV antimicrobials were not switched to PO treatment. The mean antibiotic cost per patient was €6.41 less in the intervention group in the second phase compared to the first phase. In the control group, antibiotic costs decreased by €1.69.

Implications: Implementation of a sequential antimicrobial strategy in intervention group patients led to a significant reduction in the duration of IV therapy with a significant improvement of timeliness of the switch when compared to the control group. This demonstrates the successful introduction of a pharmacist-led and delivered antimicrobial stewardship strategy, with the support of a multidisciplinary antimicrobial committee, and shows the utility of introducing structured guidelines into a hospital setting. This study also confirms the important role clinical pharmacists can play in antimicrobial stewardship strategies within the multidisciplinary team.

Background and Methods: Patients were excluded from the study if they died within 72 hours of admission, were transferred to a critical care ward, if a prolonged course of intravenous antimicrobials was required or if the antimicrobial required had no suitable oral alternative. Empiric antimicrobial prescribing guidelines were developed in-house by the hospital's antimicrobials stewardships committee that incorporated international guidelines and local antimicrobial resistance data was available to medical and pharmacy staff throughout the study period. The Mann-Whitney U test (for non-parametric data) was used to analyse all continuous variables and dichotomous variables were analysed using the chi-square test.

the Translator

Contributors
Michael Ni, BSc (Pharm) Candidate
Kenneth Tsang, PharmD Candidate
Philip Emberley, PharmD, MBA

Reviewers
Katherine Dunn
Kristina F. Goerke, MBA, CLS, MT (ASCP)
Macarena Flores Dorado
Nicole M. Acquisto, PharmD, BCPS
Christine LeBlanc, B. Journalism

Contact Information
Philip Emberley
Director, Pharmacy Innovation
Canadian Pharmacists Association
pemberley@pharmacists.ca
613-523-7877, ext. 220
1-800-917-9489
www.pharmacists.ca/research

Canadian Pharmacists Association
Association des Pharmaciens du Canada

To receive new issues of *the Translator*, contact us at **research@pharmacists.ca**