

Project: Variability in Antibiotic Use Across Ontario Acute Care Hospitals

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Background and rationale

Antimicrobial resistance, the resistance of pathogenic organisms to the antimicrobial agents designed to eradicate them, is a critical public health problem. The effectiveness of existing antimicrobials continues to weaken while the generation of novel agents has slowed. Resistant strains, whose development is accelerated by the inappropriate use of antimicrobials, are more difficult to treat and control, increasing morbidity and mortality and necessitating expensive therapies and greater healthcare expenditures. The World Health Organization (WHO), the Government of Canada, and the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada), have acknowledged the threat of antimicrobial resistance and called for greater efforts to control its ongoing and future impacts (1-3). Antimicrobial stewardship has been identified as a core intervention in addressing resistance, leveraging the surveillance of antimicrobial use practices and resistance patterns to improve the quality of prescribing.

However, the AMMI Canada 2014 report "*Surveillance of Antimicrobial Resistance and Antimicrobial Utilization in Canada*" identified major gaps in the monitoring of antimicrobial use (3). Measurement has only been conducted at the provincial level (4), with no comparisons across individual hospitals. The objective of this retrospective cohort study, which has been approved by the Research Ethics Board at Sunnybrook Health Sciences Centre and is supported by an Applied Health Research Question Grant from Knowledge Users with Public Health Ontario, is to describe and compare inpatient antibiotic use across acute care hospitals in Ontario. The results of this study may reveal significant variability in antibiotic utilization, and will be vital to inform and guide interventions to improve prescribing practices.

Methods

General study design and data sources

We will conduct a retrospective analysis of antibiotic purchasing among acute care hospitals in Ontario. Data on antibiotic purchasing has been obtained from IMS Health, an international company that provides information to the healthcare industry. Our dataset comprises the quantities of individual antimicrobials purchased per month by 160 acute care hospitals in 127 cities across Ontario, from May 1 2013 to April 30 2015. Our previous validation of this dataset found a strong correlation with internal hospital records of antibiotic dispensing (Pearson correlation coefficients of 0.90-0.98), thereby substantiating it as a valid surrogate for antibiotic consumption (Tan et al. *JAC* 2015) (5). This purchasing data will be linked, at the hospital level, to the well-validated Canadian Institutes of Health Information Discharge Abstract Database, which describes all hospitalization events in Ontario (6), through the Institute of Clinical Evaluative Sciences (ICES). Our analysis will span the 2014 calendar year.

Antibiotic purchasing will be calculated in defined daily doses (DDDs), a measure of drug use created by WHO that standardizes drug consumption based on an assumed average daily maintenance dose (7). Through linkage with the ICES administrative dataset, which includes the number of patient days admitted in calendar year 2014 at each hospital, these quantities will be given a patient days denominator.

Outcomes

The total DDDs purchased per 1000 patient-days of all antibiotics at each hospital will be the primary outcome. This will be calculated as the DDDs of antibiotics purchased by a hospital in 2014 (numerator) divided by the total patient days at that hospital in 2014 (denominator) and multiplied by 1000. Expressing antibiotic use in this way allows for standardized comparisons between hospitals. Our secondary outcomes

will include the DDDs/1000 patient-days for each individual class of antibiotics, as well as outcomes that assess antibiotic use practices of clinical significance. These include the use of broad-spectrum antibiotics, respiratory fluoroquinolones for community-acquired pneumonia, ciprofloxacin for urinary tract infections, aminoglycosides for Gram-negative infections, and antibiotics high-risk for *Clostridium difficile* infection (8, 9).

Statistical analysis

We will perform descriptive analyses to examine the characteristics of Ontario acute care hospitals, as well as the quantity and classes of antibiotics purchased. We will generate a bar graph of antibiotic purchasing at each of the hospitals over the study period, with each bar representing one hospital. We will also generate a box and whisker plot of median purchasing of individual antibiotic classes across the included hospitals, with each box representing a single class. Funnel plots will be used to examine the use of broad-spectrum and other high-risk antibiotics, and to determine whether inter-hospital variation exceeds random chance (10).

Hospitals will be classified into quintiles based on overall antibiotic purchasing. Total purchasing between the top and bottom quintiles will be compared, which will be repeated for individual antibiotic classes and for individual antibiotics. We will also compare hospital characteristics across quintiles to identify institutional factors that may affect antibiotic use, such as hospital type and location, admission composition, patient demographics and resource intensity weight.

Given increasing recognition of the importance of risk-adjustment for factors that may influence the quantity and composition of hospital antibiotic use (11-15), we will conduct a generalized linear regression of antibiotic purchasing as a function of patient and hospital characteristics at each institution. The regression equation will be used to calculate the expected quantity of antibiotics purchased at each hospital. Indirect standardization will then be performed by calculating the observed to expected ratio of antibiotic purchasing at each hospital (11, 13, 14), and the results will be presented on a bar graph and funnel plot.

All analyses will be performed using Microsoft Excel and R Version 3.2.2.

Expected outcomes and impact

Preliminary results have already demonstrated substantial variability in antibiotic use across Ontario acute care hospitals, including use of individual classes. We expect that the use of broad-spectrum and high-risk antibiotics will show similar differences. This study will, to the best of our knowledge, be the first to measure inpatient antibiotic utilization at the hospital level in Canada, and apply rigorous benchmarking methods for comparisons between hospitals. The results of this study may demonstrate the applicability of this approach in a Canadian context, leading to the use of similar methods in other provinces and in future years. The results of this study will also be useful for antimicrobial stewardship programs in Ontario to benchmark antibiotic use for intra- and inter-hospital comparisons, and will support quality improvement initiatives by clinicians and researchers to promote prudent use of antibiotics.

Upon completion of this study, the data will be linked to patient-level outcomes in order to examine the impact of variability in antibiotic utilization on important antibiotic-related outcomes, such as *Clostridium difficile* infection and colonization or infection with antibiotic-resistant organisms. This will potentially identify practices of antibiotic use associated with adverse outcomes, and guide specific stewardship interventions to improve the safety of Ontario patients.

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