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Executive Summary

In our third year, the Providence Health Care Antimicrobial Stewardship Program achieved all targets of our initial business plan. Protecting our antimicrobial resource remains an urgent health care priority. In 2015/16, the financially sustainable initiatives that facilitated optimal antimicrobial prescribing included:

» Introducing a penicillin allergy de-labeling program
» Integrating rapid molecular diagnostics with antimicrobial stewardship for patients with viral respiratory tract infections
» Creating a PHC Antimicrobial Stewardship iPhone App
» Conducting prospective audit and feedback for antimicrobial prescriptions and blood stream infections
» Participating in multidisciplinary rounds with the Division of General Surgery and the Intensive Care Unit
» Developing institutional guidelines for bacterial meningitis and septic arthritis
» Assessing all inpatient cases of laboratory confirmed *Clostridium difficile*
» Conducting a multi-site antimicrobial point prevalence survey

Continuing the dialogue on ‘Bugs and Drugs’ is important in protecting our shared antimicrobial resource.
Some measures of success included:

- Decrease in targeted antimicrobial utilization
- De-labelling penicillin allergies in 232 patients
- Sustained decrease in VRE-associated costs
- 5.8 cases/10,000 patient days
- $204,273 in antimicrobial expenditure savings

We would like to share with you the activities of the PHC Antimicrobial Stewardship Program in this report to highlight our collaborative efforts in protecting antimicrobials.
Background

We are facing an era of increasing antimicrobial resistance threats. The Antimicrobial Stewardship Program believes appropriate antimicrobial prescribing can be achieved through multifaceted approaches that engage prescribers in dialogue on “bugs and drugs,” provide relevant and timely results from diagnostic tests, and educate prescribers at the point-of-care. The ASP’s Vision and Mission guide how we effectively move towards our goal of improved health outcomes and reduced antimicrobial resistance.

VISION
To use innovative evidence-informed strategies to transform antimicrobial prescribing.

MISSION
To ensure patients and residents at Providence Health Care receive timely, effective, and safe antimicrobial therapy.
The ASP Team
Allison Kirkwood, Dr. Michelle Hinch and Dr. Victor Leung conduct the daily activities of the program. They are accountable for:

» ensuring visibility of the program across the organization.
» designing and implementing new ASP projects.
» liaising with external organizations to promote antimicrobial stewardship.
Luciana Frighetto and David Thompson provide high-level management of the program. They are responsible for:

» ensuring the ASP meets targets.
» approving program scope, resources and budgets.
» informing the Senior Leadership Team and the PHC Board of Directors on the overall status of the program.
The team | ANTIMICROBIAL STEWARDSHIP SUBCOMMITTEE

The Antimicrobial Stewardship Subcommittee meets monthly to address antimicrobial utilization topics and provide feedback on ASP guidelines.

Dr. Glen Brown
INTENSIVE CARE CLINICAL PHARMACIST AND CHAIR OF ANTIMICROBIAL STEWARDSHIP SUBCOMMITTEE

Dr. Sylvie Champagne
PHYSICIAN, DIVISION OF MEDICAL MICROBIOLOGY

Dr. Mark Hull
PHYSICIAN, DIVISION OF AIDS AND INFECTIOUS DISEASES

Dr. Michael Legal
CLINICAL PHARMACIST CTU

Dr. TC Yang
PHYSICIAN, DIVISION OF INFECTIOUS DISEASES

Dr. Chris Lowe
PHYSICIAN, DIVISION OF MEDICAL MICROBIOLOGY

Dr. Michael Payne
PHYSICIAN, DIVISION OF MEDICAL MICROBIOLOGY

Dr. Peter Phillips
PHYSICIAN AND HEAD, DIVISION OF INFECTIOUS DISEASES

Dr. Marc Romney
PHYSICIAN AND HEAD, DIVISION OF MEDICAL MICROBIOLOGY

Dr. Chantal Leger
PHYSICIAN, DIVISION OF HEMATOLOGY
Clinical Activities
Audit & Feedback

Prospective audit and feedback is fundamental to our antimicrobial stewardship activities. After reviewing the medical chart and diagnostic test results, we engage prescribers to collaboratively determine opportunities for:

» changing empiric therapy
» targeting therapy based on additional diagnostic information
» optimizing antimicrobial dosing
» determining duration of therapy
» transitioning to oral administration
» consulting infectious diseases

We leave documentation using a customized form letter generated by our database. The letter highlights our assessment and recommendation and is left in the interdisciplinary section of the chart.

Many of our clinical activities use the audit and feedback approach. We identify patients either through prescribed antimicrobials, rounds, or diagnostic test results (e.g. positive C. difficile PCR; virus detected from nasopharyngeal swab; positive blood stream infection)

Did you know?
In the last 3 years, we have made over 3500 interventions with an acceptance rate of more than 80%
Penicillin allergy de-labeling

Antibiotic allergy labels are often misleading, and negatively impact antibiotic utilization and patient outcomes. At PHC, approximately 15% of hospitalized patients are labeled as penicillin allergic. The overestimated cross-reactivity among beta-lactam antibiotics perpetuates further errors in allergy labeling.

We developed a simple questionnaire to help clarify penicillin allergy labels and triage patients who required further testing to rule out anaphylactic reactions. In partnership with physicians in the Division of Allergy and Immunology, we implemented a successful penicillin allergy de-labeling program.

We de-labeled penicillin allergy in 232 patients either through history alone, or with the addition of skin testing and oral penicillin challenge.

Did you know?
Inaccurate penicillin allergy labels are common and negatively impact patient outcomes and antibiotic utilization. Use our locally developed questionnaire to help clarify penicillin allergies.
Integrating rapid molecular diagnostics with antimicrobial stewardship for patients with viral respiratory tract infections

During the viral respiratory season, we assessed 92 patients diagnosed with a viral respiratory tract infection based on rapid molecular testing. 68% of these patients were on concurrent antibacterial treatment.

Our recommendations were accepted in 51 patients:

» 67% of these interventions resulted in discontinuing concurrent antibiotics
» 33% of interventions resulted in changing from intravenous to oral antibiotics.

We plan to continue with reviewing viral respiratory tract infection cases next year to target excessive antibacterial prescriptions in patients who are admitted with viral respiratory infections.
Antimicrobial Stewardship iPhone App

We developed a customized Antimicrobial Stewardship iPhone App containing:

» our locally developed guidelines converted to clinical decision support algorithms

» information on antimicrobials within the British Columbia hospital formulary

» recent Providence Health Care antibiogram

» content on common bacterial and fungal pathogens

» direct phone connection to the ASP pharmacist or physician

In the fall of 2016, the phone application will be available for Android operating systems. We will be assessing usability and utilization of the phone App over the next year.

You can download the PHC ASP iPhone App [here](#).
Bloodstream infections

We work with the Medical Microbiology Laboratory to rapidly report bacteremia and fungemia results to clinical teams. The PHC Medical Microbiology Laboratory uses MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) directly from blood cultures to rapidly identify causative organisms. This is coupled with direct antimicrobial susceptibility testing to help target treatment. Compared to other hospitals, we are usually able to target antimicrobial therapy 24 hours earlier.

Did you know?

Rapid and accurate diagnostic test results can improve timeliness of appropriate antimicrobial choices. At PHC, the ASP and the Medical Microbiology Laboratory work closely together to translate test results to actionable changes.
"War on the Spore" – Clostridium difficile

Appropriate and timely management of *Clostridium difficile* infection (CDI) leads to higher cure rates, and decreases probability of transmission within hospital. We continued the “War on the Spore” collaboration with the Infection Prevention and Control team using rapid alerts to communicate diagnosis and management of inpatients with laboratory tests positive for *C. difficile*. 

*C. difficile* incidence has remained stable at 5.8 cases/10,000 patient days. This year, we showed that 11% of cases reflected asymptomatic colonization. We will be expanding our review to include outpatient cases. We want to prevent readmissions and optimize management and classification of cases as true infection versus colonization.

Did you know?

Asymptomatic *C. difficile* colonization does not require treatment. At PHC, 11% of our cases this year reflected colonization.
Antimicrobial Point Prevalence Survey

Antimicrobial point prevalence studies can help assess overall burden of antimicrobial use. Although it has many limitations, the flexibility and the limited resources required for an evaluation make it useful identifying potential problem areas for antimicrobial use. This year, we worked with trainees in the infectious diseases and medical microbiology training programs to conduct a single day antimicrobial point prevalence survey at three hospitals (St. Paul’s Hospital, Vancouver General Hospital and Surrey Memorial Hospital). Of the three facilities reviewed, St. Paul’s Hospital had the highest proportion of appropriate prescriptions based on concordance with local guidelines.
Team Rounds

INTENSIVE CARE UNIT
The ASP Clinical team meets with the ICU clinical pharmacist and the Intensive Care fellow on Tuesdays and Fridays every week to review patients prescribed antimicrobials. During these “bullet rounds” we discuss opportunities for optimizing antimicrobial treatment.

GENERAL SURGERY
The ASP Clinical team joins the weekly multidisciplinary rounds to review every patient admitted to the general surgery service. The clinical pharmacist and the ASP team help facilitate antimicrobial therapy plans to optimize treatment outcomes.
Asymptomatic bacteriuria and urinary tract infections among people in residential care homes

In 2013, we introduced a toolkit and management algorithm for urinary tract infections (UTIs) and asymptomatic bacteriuria (ASB) in PHC residential care homes. In the last three years, we have maintained a sustainable decrease in collection of unnecessary urine cultures and antibiotic treatment for asymptomatic bacteriuria.

Did you know?
Decreasing unnecessary urine cultures prevents antibiotic overuse for asymptomatic bacteriuria.
Daptomycin use evaluation

Daptomycin has become the top antibacterial expenditure for the last two years. We have also seen five cases of daptomycin non-susceptible *Staphylococcus aureus* since 2013. In all these cases, non-susceptibility developed while on daptomycin. Restriction criteria for daptomycin prescribing were last revised in 2012 and do not reflect the current reasons for daptomycin prescriptions.

We conducted a daptomycin utilization evaluation from January 2013 to December 2015. There were 229 daptomycin prescription courses for 157 patients. Daptomycin was most commonly prescribed for blood-stream infections caused by *Staphylococcus aureus* (both methicillin resistant and susceptible) and Vancomycin resistant *Enterococcus faecium*.

In cases where alternative antibiotics were reasonable, daptomycin was used because of perceived increase in adherence and possible acute kidney injury from vancomycin. The retrospective chart review limited our ability to fully capture prescriber rationale for prescribing daptomycin. The findings of this evaluation were used to help inform provincial criteria for restrictions. Next year, we plan to prospectively evaluate daptomycin utilization in both inpatient and outpatient settings at PHC.
Guidelines for Management of Acute Bacterial Meningitis in Adults

**KEY MESSAGES**
- Acute bacterial meningitis (ABM) is a medical emergency.
- Common pathogens include: Streptococcus pneumoniae, Neisseria meningitidis.
- Listeria monocytogenes can cause meningitis in the following populations: greater than 50 years of age, pregnancy, immunocompromised.
- Empiric antibiotic therapy should be started once the diagnosis of acute bacterial meningitis is suspected. Duration of therapy will depend on etiology.

**PRECAUTIONS & CULTURE**
- Initiate droplet precautions for the first 24hrs of effective antibiotic therapy.
- Collect blood culture and start empiric antibiotic therapy.

**ANTIBiotic THERAPY**
- cefTRIAxone 2 g IV Q12H PLUS vancomycin 25-30 mg/kg IV loading dose x 1 followed by 15-20 mg IV Q6H for serious β-lactam allergy replace cefTRIAxone with meropenem 2 g IV Q6H
- Dexamethasone 10 mg IV Q6H x 2 to 4 days in adults. Give 15 to 20 minutes before or with the first dose of antibiotics. Discontinue if no evidence of pneumococcal meningitis.
- Add ampicillin 2 g IV Q6H for patients who have risk factors for Listeria meningitis.
- For serious β-lactam allergy replace ampicillin with trimethoprim-sulfamethoxazole 20 mg/kg IV divided Q6H

**INDICATIONS FOR CT HEAD**
- Record opening pressure & CSF appearance.
- Send for cell count with differential, glucose, protein, gram stain and bacterial cultures.
- For suspected viral meningitis, add PCR for HSV 1/2, VZV and Enterovirus.
- For aseptic meningitis: add fungal culture, serum and CSF cryptococcal antigen, and syphilis EIA.

**LUMBAR PUNCTURE**
- CSF is clear or xanthochromic.
- No abnormalities on cytology.
- Protein 0.15 - 0.55 g/L.
- Glucose 2.5 - 3.5 mmol/L.

**CSF profile may not be typical of bacterial infection in case of partially treated meningitis.**
- Add acyclovir if CSF profile is compatible with viral meningitis.
- PCR of CSF can be negative initially in the course of HSV1 infection. Repeat LP if clinical presentation is consistent with HSV meningoencephalitis.

**FURTHER MANAGEMENT**
- Septic arthritis should be suspected in patients with acute mononucleosis.
- ALWAYS obtain synovial fluid cultures and blood cultures prior to starting antimicrobial therapy.
- Staphylococcus aureus (including MRSA) is the most common pathogen (60%), followed by Group A Streptococci.
Education & Guidelines

We focus our education delivery on treatments for common infections in hospital. Our PHC specific guidelines form the basis for our education and this year we added initial management guidelines for acute bacterial meningitis and septic arthritis. Our goal is to ensure empiric treatments are chosen appropriately, and that targeted therapy is utilized in a timely manner when diagnostic test results are available and actionable. Education opportunities in 2015 also included:

» monthly orientation rounds for trainees in General Surgery
» bimonthly noon rounds for trainees on the Clinical Teaching Unit
» monthly structured teaching for trainees on the Infectious Diseases Consultation service
» supervision of trainees in both the Medical Microbiology and Infectious Diseases postgraduate training programs
Financials

Successful implementation of ASP can be associated with substantial costs savings. A concrete measure of savings is antimicrobial expenditures. This year, antimicrobial expenditures decreased by $204,273. Despite the unanticipated increase in daptomycin use, we managed to meet our initial business plan target for a total return on investment of more than 1.05 based on concrete antimicrobial savings realized over 3 years.

Did you know?
We saved over 1 million dollars in antimicrobial costs over 3 years.

TOTAL ANNUAL ANTIMICROBIAL EXPENDITURES

A: FY 13/14 antimicrobial budget decreased by $174K
B: FY 14/15 antimicrobial budget decreased by 208K
C: FY 15/16 antimicrobial budget decreased by $196K
CUMULATIVE ANTIMICROBIAL EXPENDITURES PER FISCAL PERIOD

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Drug Utilization

The following pages contain detailed drug utilization graphs.

**METHODOLOGY**

Information on antibiotic use from April 1, 2005 to March 31, 2016, was obtained from the pharmacy information system as World Health Organization defined daily doses (DDDs). The DDDs were available by fiscal period (13 periods per year, beginning in April). Patient census data was used to standardize the data to DDDs per 1000 patientdays. The Antimicrobial Stewardship Program was fully implemented in July 2013 and the period before this was used as the control.

**STATISTICAL ANALYSIS**

We conducted an interrupted time series analysis using methods previously described. Time series analysis differs from a regression analysis as values in a time series can be dependent on previous values (autocorrelated). Performing a regression analysis without accounting for autocorrelation results in inappropriate estimation of coefficients and statistical significance. We account for autocorrelation using a simple ARIMA model. Some models were found to have seasonal autocorrelation and this was also included in the model. We generated models for both St. Paul’s Hospital (SPH) and Mount Saint Joseph Hospital (MSJ) for the following antimicrobials:

1. All Antibiotic Use (defined as IV/ Oral medication with the WHO ATC classification of J01 (Antibacterials for systemic use)
2. Piperacillin/Tazobactam
3. Meropenem
4. Vancomycin IV
5. Ceftriaxone
6. Daptomycin
7. Azithromycin PO Proportion (Ratio of PO to total systemic usage)
8. Ciprofloxacin PO Proportion (Ratio of PO to total systemic usage)
9. Moxifloxacin PO Proportion (Ratio of PO to total systemic usage)
A simple interrupted time series analysis can be specified using the equation $Y_t = B_0 + B_1 t + B_2 X_1 + B_2 t_{after}$

- $Y_t$ = the outcome value
- $B_0$ = starting point/intercept
- $B_1, B_2$ = regression coefficients
- $X_1$ = Binary indicator of whether the time period is from before or after the intervention was implemented
- $t$ = number of fiscal periods since the onset of observation (13 fiscal periods/year)
- $t_{after}$ = number of fiscal periods since the onset of the intervention

The majority of the drugs that we modeled had the following regression coefficients.

- $B_0$ is the baseline DDD for the drug
- $B_1$ represents the underlying trend in DDD prior to the intervention
- $B_2$ represents the immediate change in DDD with the intervention
- $B_3$ represents the change in the DDD trend after the intervention (the sum of $B_1$ and $B_3$ is the post-intervention slope)

Some drugs (ceftriaxone and piperacillin-tazobactam) had had significant changes in usage during the time period investigated for reasons other than ASP. To model the effects correctly, additional time periods were included in the analysis. The time-series analysis was performed using R statistical software and the forecast package.
ASP was fully implemented in period 3, fiscal year 2014. There has been no significant change in overall usage of antibiotics with WHO ATC J01 Classification.
After implementation of ASP in period 3, fiscal year 2014, there was no significant change in Vancomycin usage at MSJ. However, there was a significant decrease in Vancomycin usage at SPH.
At the end of fiscal year 2009, there was a change in Piperacillin/Tazobactam restrictions resulting in increased usage at SPH. This change was incorporated into the model to appropriately fit the data. After implementation of ASP in period 3, fiscal year 2014, there was a significant decrease in Piperacillin/Tazobactam usage at MSJ and SPH.
The percentage of PO (oral) to total Azithromycin usage did not change significantly before and after implementation of ASP.
Since fiscal year 2010, there has been a significant increasing trend in Daptomycin use at SPH. No modeling of daptomycin usage was done at MSJ because of intermittent and low usage.
The percentage of PO (oral) to total Ciprofloxacin usage did not change significantly before and after implementation of ASP.
Three significant factors resulted in change in Ceftriaxone usage. These were included in the model:

- In period 3, fiscal year 2008, Ceftriaxone became the standard 3rd generation cephalosporin on our formulary.
- In Period 7 fiscal year 2012, probenecid was discontinued from the market resulting in increased ceftriaxone usage in place of Cefazolin + Probenecid for skin and soft tissue infections.
- ASP was implemented in period 3, fiscal year 2014. There has been no significant change in Ceftriaxone usage at MSJ and SPH.
The high variability in Meropenem use at MSJ precluded us from performing modeling of the data. At SPH, after implementation of ASP in period 3, fiscal year 2014, there was a significant decrease in Meropenem usage.