Focus on antimicrobial resistance

Perspectives of current and future pharmacy practices in Canada

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Disclosures

- None to declare.
Learning objectives

- Explain the global problem of antimicrobial resistance and its impact on disease.
- Identify pathways, mechanisms and causes of antimicrobial resistance.
- Describe the most prevalent and concerning patterns of resistance that are emerging in Canada.
- Describe the strategies and roles of healthcare professionals in minimizing/controlling the spread of antimicrobial resistance.
- Identify resources that provide guidance on best practices as it relates to antimicrobial resistance.
Concepts of antimicrobial resistance

- Genetic development of antimicrobial resistance
- Selection of resistance in a single patient
- Emergence of resistance in a population
- Laboratory testing for resistance
- Empiric drug selection
- Drug therapy adjustment according to sensitivity testing
- Infection control and antimicrobial stewardship for institutions and the community
Antibiotic era

- Infectious diseases as cause of mortality
  - Close to 50 per cent of deaths due to infectious diseases in early 1900s in North America
  - 25 per cent related to influenza and pneumonia
  - 25 per cent related to tuberculosis

- Therapeutics, environmental hygiene, sanitary condition
  - Infectious diseases now only related to five per cent of deaths

Crude infectious disease mortality rate in the United States from 1900 through 1996

Antibiotic era: Coming to an end?

- New molecules for antibiotic therapy
- At the FDA, of the 506 new registrations for investigational drugs only six were for antibiotics
Development of resistance

- Susceptible pathogen
  - Mutation of genetic material
  - Transfer of genetic material
  - Pathogen with one or more mechanisms of resistance

- Resistance coded on nucleus
- Resistance coded on plasmid

Also see: http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/ucm134359.htm
Mechanisms of resistance to antibiotics

- DNA replication
- Nucleotide biosynthesis
- Protein synthesis
- Topoisomerase
- mRNA transcription
- Protein synthesis
- mRNA
- Protein
- Ribosomal protection (e.g., tet proteins)
- Elimination or overproduction of antibiotic target
- Enzymatic inactivation (e.g., β-lactamase)
- Mutational events
- Genetic material from external sources (e.g., plasmids)
- Efflux pumps
- Decreased cell wall permeability
- Elimination or overproduction of antibiotic target

Adapted from: Chopra I. Curr Opin Pharmacol 2001;1:464
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Discovery of antimicrobials and emergence of resistance

- **1930**: Penicillin
- **1940**: Chloramphenicol
- **1950**: Erythromycin
- **1960**: Cephalosporins
- **1970**: Vancomycin
- **1980**: Ciprofloxacin
- **1990**: Norfloxacin
- **2000**: Azithromycin, Clarithromycin, Levo
- **2010**: Gatifloxacin, Moxifloxacin

Organisms and resistances:
- Shigella, multidrug resistance
- S. aureus, Methicillin
- E. coli, Ampicillin
- S. pneumoniae, Penicillin
- Salmonella, Ampicillin
- H. influenzae, Ampicillin
- M. tuberculosis, mdr S. pneumoniae, Cipro /Levo

Canadian Pharmacists Conference 2015
Innovation and Collaboration

Jointly presented by
Canadian Pharmacists Association
Association des Pharmaciens du Canada
Ontario Pharmacists Association
Association des Pharmaciens de l’Ontario
Overall MRSA rate in Canada 1995-2009

MRSA: Methicillin Resistant Staphylococcus aureus
Canadian Nosocomial Infection Surveillance Program
Overall MRSA rate per region 1995-2009

MRSA: Methicillin Resistant Staphylococcus aureus
Canadian Nosocomial Infection Surveillance Program
MRSA infection rate per region 1995-2009

MRSA: Methicillin Resistant Staphylococcus aureus
Canadian Nosocomial Infection Surveillance Program
Invasive *S. pneumoniae* infection surveillance LSPQ 2012

<table>
<thead>
<tr>
<th>Antibiotiques</th>
<th>2008 (n = 370)</th>
<th>2009* (n = 449)</th>
<th>2010 (n = 394)</th>
<th>2011 (n = 328)</th>
<th>2012† (n = 336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pénicilline G – critère ménine</td>
<td>17,6</td>
<td>18,5</td>
<td>12,7</td>
<td>13,1</td>
<td>12,2</td>
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<tr>
<td>Pénicilline G – critère non ménine</td>
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<td>0,5</td>
<td>1,5</td>
<td>0,6</td>
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<td>Chloramphénicol</td>
<td>3,5</td>
<td>1,8</td>
<td>2,0</td>
<td>1,5</td>
<td>0,6</td>
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<td>Érythromycine</td>
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<td>20,3</td>
<td>18,3</td>
<td>15,9</td>
<td>23,2</td>
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<tr>
<td>Clindamycine</td>
<td>17,6</td>
<td>15,4</td>
<td>14,7</td>
<td>13,7</td>
<td>15,5</td>
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<tr>
<td>TMP-SMX</td>
<td>4,9</td>
<td>5,3</td>
<td>3,1</td>
<td>3,7</td>
<td>3,3</td>
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<tr>
<td>Vancomycine</td>
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<tr>
<td>Lévofoxacine</td>
<td>0,3</td>
<td>0,7</td>
<td>0,5</td>
<td>0,5</td>
<td>0,0</td>
</tr>
</tbody>
</table>

* En 2009, aucune croissance pour une souche lors de la réalisation des antibiogrammes.
† En 2012, aucune croissance pour une souche lors de la réalisation des antibiogrammes.

Identified hospitals for detection, Laboratoire de Santé Publique du Québec (LSPQ)
Invasive *S. pneumoniae* infection surveillance LSPQ 2012

Identified hospitals for detection, Laboratoire de Santé Publique du Québec (LSPQ)
Emerging macrolide use associated with azithromycin resistance

 Resistance to macrolides (%) vs. Azithromycin use (% of macrolides)

R = 0.9659  
P < 0.0001

Davidson et al ECCMID 2003
**C. difficile** strain in North America

- Strain identified in Pittsburg, CDC in 1999
- Binary toxin with partial loss of the tcdC gene (BI/NAP1 toxinotype III)
  - 84 per cent of cases in the 12 hospitals evaluated in Montreal

Loo et al. NEJM 2005;353:2442-9; McDonald LC et al. NEJM 2005; 353: 2433-41.
Annual incidence of CDAD in southern Quebec up to 2003

Annual incidence per 100,000 patient days of CDAD 1991-2003

Pépin et al. CMAJ 2004

n = 1721
Clostridium difficile infection, incidence, attributable mortality and fraction of NAP1 strain (per province)


BC, British Columbia; CDAD, C. difficile–associated disease; Sask/Man, Saskatchewan and Manitoba.
Impact of antimicrobial resistance

- Antimicrobial-resistant pathogens affect patient outcomes in several ways:
  - Treatment factors
    - Delay in appropriate antimicrobial treatment
    - Decreased antimicrobial effectiveness
    - Increased antimicrobial toxicity
    - Improper antimicrobial dosing
  - Increased need for surgery/invasive procedures
  - Increased length of stay in hospital
  - Increased mortality rates

Cosgrove SE. Clin Infect Dis 2006:42 (Suppl 2)
Attributable costs, excess lengths of stay and risk of mortality associated with various antimicrobial-resistant pathogens

<table>
<thead>
<tr>
<th>TYPE OF ANTIMICROBIAL-RESISTANT INFECTION</th>
<th>INCREASED RISK OF DEATH (OR)</th>
<th>ATTRIBUTABLE LOS (DAYS)</th>
<th>ATTRIBUTABLE COSTS (US$)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA bacteremia</td>
<td>1.9</td>
<td>2.2</td>
<td>$6,916</td>
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<tr>
<td>MRSA surgical infection</td>
<td>3.4</td>
<td>2.6</td>
<td>$13,901</td>
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<tr>
<td>VRE infection</td>
<td>2.1</td>
<td>6.2</td>
<td>$12,766</td>
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<tr>
<td>Resistant <em>Pseudomonas</em> infection</td>
<td>1.8-5.4</td>
<td>5.7-6.5</td>
<td>$11,981-32,949</td>
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<td>Resistant <em>Enterobacter</em> infection</td>
<td>5.0</td>
<td>9</td>
<td>$29,379</td>
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<tr>
<td>Resistant <em>Acinetobacter</em> infection</td>
<td>2.4-6.2</td>
<td>5-13</td>
<td>$3,758</td>
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<tr>
<td>ESBL or KPC-producing <em>Escherichia coli</em> or <em>Klebsiella</em> infection</td>
<td>3.6</td>
<td>1.6 fold increase</td>
<td>1.7 fold increase</td>
</tr>
</tbody>
</table>

Impact of bacterial resistance

Leads to increased rates of morbidity and mortality

Hospital mortality and infection related mortality rates for infected patients from all causes (n=655) receiving either initially inadequate or adequate antimicrobial treatment.

Importance of initial empiric antibiotic selection in the ICU

Crude or infection related mortality
Impact of appropriate antimicrobial therapy for septic shock

Appropriate therapy in 80% of pts. Five fold reduction in mortality with appropriate therapy (From 52% to 10% OR 9.45 CI 7.74-11.54 p<0.0001)

Antimicrobials is the class of medication most used in hospitals in Canada

<table>
<thead>
<tr>
<th>% of medication acquisition costs of hospitals dedicated to antimicrobials for fiscal year 2004-2005</th>
<th>National average</th>
<th>Provincial average</th>
</tr>
</thead>
<tbody>
<tr>
<td>9%</td>
<td>6% to 14%</td>
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</tbody>
</table>

Factors that may increase antimicrobial resistance in hospitals

- Greater severity of illness of hospitalized patients
- More severely immunocompromised patients
- Newer devices and procedures in use
- Increased introduction of resistant organisms from the community

Factors that may increase antimicrobial resistance in hospitals

- Ineffective infection control and isolation practices and compliance
- Increased use of antimicrobial prophylaxis
- Increased empiric polymicrobial antimicrobial therapy
- High antimicrobial usage per geographic area per unit time

Interventions to overcome bacterial resistance

- Adjust pharmacotherapy
  - Increase spectrum of activity in empiric therapy (new agents)
  - Combination therapy
  - Increase dose of agents (amoxicillin)
- Prevent emergence of resistance during treatment (combination therapy)
- Prevent transmission of resistance between patients
- Prevent development of resistance within institutions and populations

Canadian Centre For Antimicrobial Resistance (CCAR 1998-2009)

- A coordinating and advocacy group to control the development and spread of antimicrobial resistance
- Advocates for, facilitates, promotes programs related to surveillance, optimal antimicrobial use and infection prevention and control to limit antimicrobial resistance

## CCAR organization

### Mapping the Canadian practice: Selected examples.

<table>
<thead>
<tr>
<th>Organization</th>
<th>Education/ Knowledge Translation</th>
<th>Surveillance Research</th>
<th>Intellectual Capital</th>
<th>Stewardship</th>
<th>Advocacy</th>
<th>Getting issues on Govn’ t agenda</th>
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<td>AMMI</td>
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</tbody>
</table>

CHEC: Canadian Hospital Epidemiology Committee  
CADTH: Canadian Agency for Drugs and Technology in Health  
AMMI: Association of Medical Microbiologists and Infectious Disease Canada  
CSHP: Canadian Society of Hospital Pharmacists  
CAHI: Canadian Animal Health Institute  
CPS: Canadian Patient Safety Institute
CARA is a research group dedicated to the study of medical microbiology/infectious diseases issues with special interest in infections caused by antimicrobial resistant pathogens as well as antimicrobial usage in Canada.

www.can-r.ca
Safer Health Care Now
Launched in 2005

- SHN is a patient safety initiative aimed at reducing preventable adverse events and deaths in Canadian healthcare

- Ten Priorities (Phase I and II)
  - Antimicrobial Resistant Organisms with *Staphylococcus aureus*
  - Central Line Infections Prevention
  - Ventilator Associated Infections Prevention
  - Surgical Site Infections Prevention
Provincial community empiric therapy recommendations

Conseil du médicament, gouvernement du Québec, Canada

www.INESSS.gouv.qc.ca
Optimize antimicrobial use through appropriate selection, dosing, route and duration of antimicrobial therapy that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.

Antimicrobial stewardship

- **Goals**
  - Optimize clinical outcomes
  - Minimize unintended consequences (toxicity, selection of pathogens, emergence of resistance)

- **Benefits**
  - Improved patient safety
  - Reduce *C. difficile* rates in conjunction with other interventions
  - Direct savings on acquisition costs
  - Decreased healthcare costs through improved outcomes

Framework for optimal antimicrobial use in institutions

- Preserve antimicrobial efficacy for treatment of infections by delaying the development of resistance
- Improve antimicrobial prescribing in general and avoid toxicity and adverse events
- Involve and support all concerned parties
- Understand how resistance develops in institutions

www.inesss.qc.ca
Empiric antimicrobial therapy handbook

- Aimed at optimizing antimicrobial use
- Guide to diagnosis
- Empiric treatment algorithms
- Based on regional resistance patterns
- Updated every 4 years

www.publicationsprism.com
Getting involved

- Direct patient care
  - Prevention
  - Treatment
- Pharmacists have a global perspective of patient care through antimicrobial use
  - Can identify opportunities for intervention
  - Need to take ownership of drug use measurement
Summary: The pharmacist’s role

- Direct patient care: wards, pharmacies
- Pharmacometrics (kinetics, monitoring)
- Local guidelines
- Data analysis on drug use (DDD)
- Institutional interventions (Safer Health Care Now!)
- National Independent Initiatives (CAN-R, CNISP, CSHP-IDPSN)
- Government policies (CCAR, INESSS, ASP initiatives)
- Research