Antimicrobial Utilization and Stewardship: Human Medicine Perspectives

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Panacea to Preservation

Source: Google Images
Disclosures

- Clinical reviewer and co-investigator: CADTH (C. difficile and MRSA projects)
- Grants: AI-HS, PHAC, Alberta Health, AHS, Exciton, CIHR
- Speaker or Meeting Participant (last 3 years): Pfizer (new antibacterials), bioMerieux (healthcare infections), Sanofi (C. difficile burden of illness), Merck (monoclonal Abs)
- Member: WHO AGI SAR, GI PC Network
Objectives

- Outline the frequency and impact of antibiotic use
- Review the general background on antibiotic utilization and stewardship
- Describe the evidence base to support stewardship as a means to improve patient safety and quality of care
- Provide the Canadian context for utilization and stewardship
Antimicrobial Use

- **Therapeutic**
  - Life threatening situations
  - Potentially life threatening

- **Prophylaxis**
  - Non-life threatening – easier to alter physician prescribing behaviour
  - Accounts for up to 30% of antibiotic use

- **Other**
  - Anti-inflammatory, prokinetic, fatigue of chronic lyme
Frequency of Use of Antimicrobials

- Antimicrobials are among the most commonly used class of drugs in Canadian hospitals.
- Pharmacy expenditures – represent a significant proportion of an institution’s total budget.
- 55.7% of patients discharged from 323 hospitals in the US in 2010 received antibiotics during their hospitalization.
- Recent 2015 point prevalence survey Calgary hospitals: 30% of patients on antimicrobials.

5 Principles of Antibiotic Resistance

1. Given sufficient time and drug use, antibiotic resistance will emerge – resistance has arisen to every antibiotic.

2. Resistance is progressive – evolving from low levels through intermediate to high levels.

3. Organisms resistant to one drug are likely to become resistant to others.

4. Once resistance appears it is likely to decline slowly if at all.

5. The use of antibiotics by one person affects others in the immediate and extended environments.

Levy SB NEJM 1998;338:1376-1378
methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC (US).

**Antibiotic resistant organisms are increasing.** New antibiotic drug development is rapidly decreasing.\(^1\)

A perfect storm for an infectious disease catastrophe.

**Source:** Spellberg et al., *Clinical Infectious Diseases*, May 1, 2004 (modified)
Common Measures of Antimicrobial Utilization

1. DDD/1000 pt days
   - WHO standard; no patient level data; easy to calculate; facilitates intercountry comparisons
   - Reference DDDs may not = given dose; not for pediatrics

2. DOT/1000 pt days
   - Not affected by changes in WHO reference DDDs; useful for pediatrics; incorporates LOS
   - No dosage measure; requires patient level data; undercalls renal dosing

3. LOT/1000 pt days
   - Useful for units; requires patient level data

4. Others: COT/LOT ratios; % receiving/admissions; kg used; PDDs
Antimicrobial Stewardship - Definition

“The optimal selection, dosage, and duration of antimicrobial treatment 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 - Definition

■ In Canada antimicrobial stewardship is considered to be the responsible planning and management of resources in order to prevent and moderate the development of antimicrobial resistance

■ May consider from multiple perspectives – clinical, public health, systems, governance
  ✗ human and animal settings

Public Health Agency of Canada, Centre for Communicable Disease and Infection Control Stewardship Task Group Report 2016
Antimicrobial Stewardship Programs

- **Quality improvement and patient safety**
  - Improve quality of medical care
  - Reduce adverse events and allergies

- **Collateral damage reduction**
  - Prevention of resistance by selection for drug-resistant organisms [ESBLs, MRSA, VRE]
  - *C. difficile*; AAD; unwanted colonization with MDROs)


- **Cost containment**
  - Reduction in antimicrobial costs
  - Clinical and economic burden of antibiotic resistance

Collateral Damage: Association of Antibiotics with CDAD in Quebec

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Period: incidence per 1000 patient-days of antibiotic use*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow-spectrum penicillins</td>
<td>1.4 (28/19908)</td>
</tr>
<tr>
<td>β-lactam/β-lactamase inhibitors</td>
<td>1.0 (7/7267)</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
</tr>
<tr>
<td>First-generation</td>
<td>2.3 (30/12779)</td>
</tr>
<tr>
<td>Second-generation</td>
<td>3.9 (55/13984)</td>
</tr>
<tr>
<td>Third-generation</td>
<td>2.7 (18/6786)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>2.7 (7/2553)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>2.4 (21/8673)</td>
</tr>
<tr>
<td><strong>Quinolones</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6 (48/29693)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>4.9 (19/3861)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>1.9 (5/2625)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2.0 (20/10092)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2.5 (9/3658)</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>0.2 (8/51706)</td>
</tr>
</tbody>
</table>

*Calculated from numbers in parentheses; the numerator represents the number of patients with hospital-acquired CDAD who received a given class of antibiotic during the 2 months before diagnosis, and the denominator represents the total number of patient-days that this class of antibiotic was used among all inpatients.

Pepin J et al. CMAJ 2004;171:466-472
Failure of Infection Control Measures - Reduction in CDAD with Targeted Antibiotic Consumption Intervention

Antimicrobial Stewardship Policies

Persuasive

- Education for prescribers
  - Conferences
- Peer Review
  - Utilization review with feedback
- Tailoring or de-escalation of therapy
- Academic detailing
  - Face to face presentations
- Therapeutic guidelines
  - National, regional, local
- Sequential antimicrobial therapy (IV to oral conversion)
- Computer assisted decision support

Antimicrobial Stewardship Policies

Restrictive

- Cascade susceptibility reporting
- Controlled formulary
- Automatic stop orders
  - IV vs. oral
- Automatic therapeutic interchange
- Restricted antimicrobial agents
  - Approval necessary a priori vs. concurrent review and feedback
- Antibiotic order forms
- Infectious Diseases consultations

Establishing an Antimicrobial Stewardship Program

- Multiple guidelines exist in the literature
  - IDSA guidelines for developing an institutional program to enhance antimicrobial stewardship
    Clin Infect Dis 2007;44: 159–177
  - Policy statement on antimicrobial stewardship
    Infect Control Hosp Epidemiol. 2012;33:322-7
  - Guidance for the knowledge and skills required for antimicrobial stewardship leaders
    Infect Control Hosp Epidemiol. 2014 35(12):1444-51
  - Implementing an antibiotic stewardship program: IDSA evidence based guideline
Components of an Antimicrobial Stewardship Program

- **Minimum Requirements**
  - Core multidisciplinary team formation
  - Formulary with restrictions
  - Guidelines relevant to the facility and preauthorization for certain agents
  - Measure and monitor antimicrobial use
  - Provision of local antibiograms

- **Core and Supplemental Strategies**
  - **Core**: Formulary restrictions and prospective audit and feedback
  - **Supplemental**: education, pathways, de-escalation, iv to oral stepdown, others
Tailoring or De-Escalating Antimicrobials

- Based on natural history of clinical phases of illness
- Acute $\rightarrow$ Subacute $\rightarrow$ Convalecent phase
- Empiric antibiotics in acute phase
- Entry to subacute phase about 72-96 hours
- Susceptibilities arrive 48-72 hours
- Timing at Day 3 ideal as process measure to tailor or de-escalate

Clinical Benefits of Sequential Antibiotic Therapy

- Earlier discontinuation of IV
  - Increased patient comfort
  - Decreased risk of complications
- Enhanced mobilization
- Reduced risk of nosocomial infection
- Earlier discharge from hospital
- Improved quality of life
You wouldn’t like me when I’m angry...

Because I always back up my rage with facts and documented sources.

-The Credible Hulk
Evidence Base to Support Antimicrobial Stewardship

- **Reduction in antimicrobial resistance**
  - Finland’s consumption of macrolide antibiotics decreased from 2.40 defined daily doses/1000 inhabitants/day in 1991 → 1.38/1000 inhabitants/day in 1992 (p=0.007) and continued to 1996 due to national guidelines.
  - With decrease in consumption - ↓ in erythromycin resistance of Gr. A streptococci from throat swabs – 16.5% (1992) → 8.6% (1996)

Seppala H et al. N Engl J Med 1997;337:441-446
Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis

Emelie C Schots, Marlies E J L Hulscher, Johan W Mouton, Cees M Verduin, James WT Cohen Stuart, Hans WPM Overdiek, Paul D van der Linden, Stephanie Natsch, Cees MPM Hartogh, Tom FW Wolfs, Jeroen A Schouten, Bartjan Kullberg, Jan M Prins

Summary
Background Antimicrobial stewardship is advocated to improve the quality of antimicrobial use. We did a systematic review and meta-analysis to assess whether antimicrobial stewardship objectives had any effects in hospitals and long-term care facilities on four predefined patients' outcomes: clinical outcomes, adverse events, costs, and bacterial resistance rates.

Methods We identified 14 stewardship objectives and did a separate systematic search for articles relating to each one in Embase, Ovid MEDLINE, and PubMed. Studies were included if they reported data on any of the four predefined outcomes in patients in whom the specific antimicrobial stewardship objective was assessed and compared the findings in patients in whom the objective was or was not met. We used a random-effects model to calculate relative risk reductions with relative risks and 95% CIs.

Findings We identified 145 unique studies with data on nine stewardship objectives. Overall, the quality of evidence was generally low and heterogeneity between studies was mostly moderate to high. For the objectives empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation the overall evidence showed significant benefits for one or more of the four outcomes. Guideline-adherent empirical therapy was associated with a relative risk reduction for mortality of 35% (relative risk 0.65, 95% CI 0.54–0.80, p<0.0001) and for de-escalation of 66% (0.44, 0.30–0.66, p<0.0001). Evidence of effects was less clear for adjusting therapy according to renal function, discontinuing therapy based on lack of clinical or microbiological evidence of infection, and having a local antibiotic guide. We found no reports for the remaining five stewardship objectives or for long-term care facilities.

Interpretation Our findings of beneficial effects on outcomes with nine antimicrobial stewardship objectives suggest they can guide stewardship teams in their efforts to improve the quality of antibiotic use in hospitals.

Effects on Mortality of Stewardship Components

De-escalation (Forest Plot)  Prescribing empiric therapy based on guidelines (Forest plot)

Guideline-adherent empirical therapy RRR for mortality of 35% (relative risk 0.65, 95% CI 0.54–0.80, p<0.0001)
and for de-escalation of 56% (0.44, 0.30–0.66, p<0.0001)
Stewardship in ICU—Systematic Review

- Any experimental intervention (any type stewardship) to improve antimicrobial utilization in ICU
- 24 studies met inclusion criteria; 2 de-escalation, 3 RCTs, 3 ITS & 18 uncontrolled before-after studies

Outcomes
- Reductions in antimicrobial utilization (11%–38% DDD/1000 pt-days)
- Lower total antimicrobial costs (US $5–10/patient-day)
- Shorter average duration of antibiotic therapy, less inappropriate use and fewer antibiotic adverse events
- Stewardship > 6 months associated with ↓ antimicrobial resistance rates and no change NIs, LOS or mortality

De-escalation in ICU

- Cohort study on the safety and impact on in hospital and 90-day mortality of antibiotic de-escalation in patients admitted to the ICU with severe sepsis or shock (n=628)

- De-escalation in 219 patients;
  - By MV analysis, independent RF associated with in-hospital mortality were septic shock, SOFA score the day of culture, inadequate empirical antimicrobial therapy
  - **De-escalation was a protective factor [OR 0.58; 95 % CI 0.36-0.93]**

- Why? Less toxicity; NI; collateral damage

Effectiveness of Antimicrobial Stewardship Policies

- Based on evidence most effective interventions appear to be restrictive administrative methods including formulary control applied at the institution or provincial level

Antimicrobial Utilization and Stewardship in the Canadian Setting

- Historic issues
- Public Health Agency of Canada initiatives
- Accreditation Canada
- Provincial initiatives
- Local Initiatives
Stewardship in the Canadian Setting

Historic overview

- 1997 Canadian Consensus Conference "Controlling antimicrobial resistance. An integrated action plan for Canadians” recommendations
  - establish antibiotic stewardship and antibiotic use teams in all Canadian hospitals by:
    a. using accreditation standards
    b. obtaining support from administrative leadership
  - establish antimicrobial use, monitoring, and intervention programs

  - obtain, analyze and disseminate data/information on antibiotic use in humans and animals

Stewardship in the Canadian Setting

Historic overview

- 2009 Pan-Canadian Stakeholder Consultations on Antimicrobial Resistance
  - develop a universally agreed to definition of stewardship ….
  - develop a coordinated integrated inter-disciplinary Pan-Canadian approach….
  - develop and promote public and professional awareness of antimicrobial stewardship responsibilities and concerns

- 2014 Senate Briefings; NCCID Report of Antimicrobial Resistance and Antimicrobial Utilization in Canada; Accreditation Canada ROP; Federal Framework for Action

- 2015 Auditor General Report AMR in Canada

Rennert-May E, Conly J Antimicrobial Stewardship: A Canadian Perspective. 2016. Intern J Health Gov
Available AMU Data Canada

- IMS Brogan Products:
  - Canadian Drug Store & Hospital Purchases (CDH)
  - Canadian CompuScript (CSC)
  - Canadian Disease and Therapeutic Index (CDTI)
  - Retail Prescription

- First Nations and Inuit Health Branch (FNIHB)
  - Non-insured prescription

- CNISP Hospital-based antimicrobial usage

Courtesy PHAC CNISP Kahina Abdesselam
Metrics for monitoring use

**Prescription rates**

- **Prescriptions per 1,000 inhabitants**

**DDD per prescription**

- **Defined daily doses per 1,000 inhabitants**

**DDD rates**

- **DDDs per prescription**

**Total kilograms of active ingredient**

- **Total kilograms**

Courtesy PHAC CNISP Kahina Abdesselam
– Approximately 40 sites participating (missing quite a few AMU data)
– 3 pediatrics stand alone participating in 2015 but potentially only 2 participating in 2016
– Variables collected:
  • Antimicrobial
  • Total grams administered or the administered daily dose
  • Bed size
  • Patient days
  • Calendar year
  • Route of administration
  • DOT for pediatric sites

Courtesy  PHAC CNISP Kahina Abdesselam
Overall Trend

• Antimicrobial consumption has remained stable over the last 5 yrs but 6% decrease in consumption rate
• Significant Individual drug trend over the last 5 years
  – ↑ 115% Doxycycline
  – ↑ 107% Ertapenem
  – ↑ 64% Clavulin
  – ↓ 37% Cefuroxime
  – ↓ 28% Clarithromycin
  – ↓ 21% Ciprofloxacin
• Antimicrobial consumption based on different categories of bed sizes were not significantly different over the last 5 years
  – > 500 bed size reported 573 DDD per 1,000 patient days; 200 to 500 bed size reported 653 DDD per 1,000 patient days and <200 bed size reported 1,042 DDD per 1,000 patient days
Ten most prescribed antimicrobial by DDD per 1,000 patient-days reported by CNISP participating hospitals between 2009 and 2013 in Canada

Atimicrobial Use Working Group
Canadian Noscomial Infection Surveillance Program

Courtesy PHAC CNISP Kahina Abdesselam
Accreditation Canada and Stewardship

- Antimicrobial stewardship can accomplish:
  - In combination with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria.
  - Studies also indicate that antimicrobial stewardship programs are cost effective, and provide savings through reduced drug costs and avoidance of microbial resistance.

Source: Accreditation Canada
Accreditation Canada developed a “Required Organizational Practice” (ROP) under Medication Use on Antimicrobial Stewardship in 2013.

- “The organization has a program for antimicrobial stewardship to optimize antimicrobial use”
- Applies to all acute care organizations
- Applicable as of May 2014
- Organizations should use a tailored approach consistent with their size, service environment and patient population

Source: Accreditation Canada
ROP Tests of Compliance

1. The organization implements an antimicrobial stewardship program
2. The program includes lines of accountability for implementation
3. The program is inter-disciplinary
4. The program includes interventions to optimize antimicrobial use that may include:
   - audit and feedback
   - a formulary with approved indications
   - guidelines and clinical pathways for antimicrobial utilization
   - strategies for streamlining or de-escalation of therapy
   - parenteral to oral conversion of antimicrobials
   - education
   - dose optimization
Provincial Initiatives

- **Ontario**
  - Public Health Ontario and OHA partnership to focus on stewardship within Ontario hospitals
  - Major Consensus Conference planning for stewardship

- **Quebec**
  - 2011 study from Quebec described the impact of a bundle approach on ambulatory prescribing

- **BC**
  - Multiple initiatives “Do Bugs Need Drugs”, PharmaNet utilization, BC Clinical Care Management program aims to improve stewardship

- **Alberta**
  - Alberta wide approach via its 5 zones
**Alberta Stewardship Initiatives**

**Theme:**
“Reduce Your Antibiotic Footprint”

**Current:**
- Provincial ASC
- Common formulary and TIs and restrictions
- Zone Committees roll up
- Annual AS report

**New:**
- Zone Progress Reports
- Zone Initiatives Reports
Reviewed Early/Prescribed Surely

Day 3 Bundle (D3B) for antimicrobials
Reassess initial diagnosis
Review all microbiology results
Tailor antimicrobials; choice & duration
Switch intravenous to oral route
Prospective Audit and Feedback Hospitalist Services

- Re-organization in Pharmacy allowed 4 ID trained pharmacists to conduct daily reviews all new antibiotic starts FMC hospitalists – rounds discussion or note to chart

- Rotation of ID physicians who provide daily discussion of difficult cases

- Evaluation after 1 year revealed 80% acceptance of recommendations (full or partial) and significant improvement de-escalation and conversion to po antibiotics
Spectrum

Get the right drug for the right bug at the right dose and the right duration.
Spectrum Calgary

- Spectrum is an adaptable and locally tailored antimicrobial stewardship application

- Goals:
  - To educate users on antimicrobial stewardship principles and optimal prescribing through the app experience
  - To improve the appropriate antimicrobial utilization for common infectious syndromes in hospitalized patients in Calgary
  - To expand the product in scope, location, and media and improve existing content through incorporation of user feedback in an iterative fashion
App Features

By Syndrome

SELECT ANY THAT APPLY

- Community acquired
- Hospital acquired or healthcare associated
- Healthcare Associated
- Colonized or recent infection with resistant organism (e.g. ESBL or ampC), or recent piperacillin-tazobactam use (<3mo)
- Bilirubin > 68 umol/L
- Serum Cr > 88 umol/L

SUGGESTED ANTIMICROBIAL REGIMEN

- Piperacillin-tazobactam 3.375g IV q6h
- OR
- Meropenem 500mg IV q6h
- AND
- Albumin 1.5g/kg IV at time of diagnosis and 1g/kg IV on day three reduces renal failure and mortality

FOLLOW UP

Patients with SBP should...
S P E C T R U M
(your site/region/city...)

- User friendly (above average usability)
- Iterative open source feedback
- iTunes downloadable free app for Spectrum Calgary
- Menus of options for specific site development
  - Base of antimicrobials/ pathogens/ antiobiograms
  - Optional customization of algorithms
  - Optional add local epidemiology
- Future: Android version coming and ICU outcomes evaluation completed and submitted IDSA

spectrum.md
The power to make a difference in stewardship is in your hands