ASP 101

What is Antimicrobial Stewardship?
Objectives

• To describe the rationale for antimicrobial stewardship;

• To state the definition and goals of antimicrobial stewardship;

• To identify the important aspects of an antimicrobial stewardship program;

• To discuss the evidence supporting antimicrobial stewardship programs;

• To provide a few ‘real world’ examples of antimicrobial stewardship.
Rising Antimicrobial Resistance

- Methicillin resistant *Staphylococcus aureus* (MRSA)
- Vancomycin resistant enterococci (VRE)
- MDR and extremely drug resistant (XDR) Tuberculosis
- Carbapenemase producing Enterobacteriaceae (CPE’s)
  - Examples:
    - *Klebsiella pneumoniae* carbapenemases (KPCs)
    - New Delhi metallo-β-lactamase-1 (NDM-1)

Resistant organisms result in increased morbidity, mortality and increased healthcare costs


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Overall MRSA rates, CNISP 1995-2011 (per 1,000 patient-admissions)

© Public Health Agency of Canada
Source: Canadian Nosocomial Infection Surveillance Program (CNISP), Public Health Agency of Canada. 2011.
Overall VRE rates, CNISP 1999-2011 (per 1,000 patient-admissions)

Source: CNISP 2012

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Absolute Numbers of MDR Tuberculosis Reported per Country in 2010

© World Health Organization, 2011.
Source: World health Organization 2012
Number of CPE positive isolates received by month and type of resistance in Ontario: 2008 - 2012

Source: Public Health Ontario Laboratories, Carbapenem Producing Enterobacteriaceae database, extracted by Public Health Ontario [2012/08/14]
New Delhi metallo- β-lactamase (NDM-1)

- NDM-1 was first detected in 2009 from *K. pneumoniae* and *E. coli*
  - Isolated from a patient in Sweden who had received medical care in New Delhi
- NDM-1 is not a bacterial species, but a transmissible genetic element encoding multiple resistance genes, generally found in Enterobacteriaceae
- First NDM-1 case reported in Canada in 2010
  - 32 year old man admitted to hospital in Mysore, India with hyperglycemia and urinary tract infection (UTI)
  - Transferred to a hospital in Alberta and diagnosed with prostatitis and pyelonephritis due to *E. coli* containing NDM-1
- First case reported in Ontario, also in 2010
  - 36 year old woman admitted with UTI due to *E. coli* containing NDM-1
  - Had recently travelled to Mumbai, India where she had a 2 day admission to hospital following a miscarriage.

Source:
• Example of widespread environmental reservoirs of NDM-1 in India

• NDM-1 now endemic within India and it is possible to acquire NDM-1 outside of hospitals

• At this point, it will be very difficult to contain spread of NDM-1

• Highlights the urgent need to prevent emergence of resistance
Fluoroquinolone use and correlation to ciprofloxacin resistance among uropathogens in British Columbia

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Patrick DM et al. CMAJ. 2009;180(4):416-21

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Dramatic Drop in Development and Approval of Antimicrobial Agents

Approach to Reducing Antimicrobial Resistance: Multi-pronged Approach

1. Infection prevention and control
   • Minimize spread of resistant organisms

2. Improve diagnostics (i.e. respiratory infections)
   • Help eliminate use of antibiotics in non-bacterial infections
   • Improve recovery of causative pathogens and their susceptibilities to help healthcare workers narrow antimicrobials

3. Continued development of antimicrobials for use for highly resistant pathogens

4. Reduce resistance reservoirs (i.e. environmental and livestock)

5. Antimicrobial stewardship programs

Antibiotic Stewardship Defined

“Coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration.”

SHEA; IDSA; PIDS. Infect Control Hosp Epidemiol. 2012;33(4):322-7
Bottom Line: Antimicrobial Stewardship

- After confirming that the patient has an indication for antimicrobial therapy, antimicrobial stewardship is the:
  - **Right drug**, at the
  - **Right time**, using the
  - **Right dose**, and
  - **Right duration**

Goals of an Antimicrobial Stewardship Program

• Optimize patient safety
  • Achieve best clinical outcomes related to antimicrobial use
  • Minimize toxicity and other adverse events related to antimicrobial use

• Reduce resistance
  • Limit selective pressure on antimicrobial populations

*ASPs may also reduce costs associated with suboptimal antimicrobial use but this is not the primary goal of an ASP

Antimicrobial Stewardship: Not Just for Hospitals

• To date most ASPs have been focused in hospitals
• To curb antimicrobial resistance, ASPs will have to apply to community healthcare settings and long-term care facilities
• In general, most hospitals tend to start their ASP within the hospital setting and extend outwards
What does an Antimicrobial Stewardship Program Look Like?

• No ‘one size fits all’ See ‘Getting Started’ Gap Analysis Tool

• ASPs should be tailored to each hospital and depends on:
  • Hospital size
  • Resources
  • Local antimicrobial prescription and resistance patterns
  • Patient population

• Each hospital needs to define how their facility can best meet the objectives of an ASP

Antimicrobial Stewardship Program: The Team

- ASP team members should include (but are not limited to):
  - Physician
    - Typically an ID physician where possible, but could also be a hospitalist, internist, emergency room physician, family doctor or other
  - Needs to be a stewardship champion
  - Pharmacist
    - Ideally has ID training (formal or informal)
  - Clinical microbiology laboratory services
  - Infection prevention and control

Antimicrobial Stewardship Program: 
The Team

• Ad hoc team membership can include (but is not limited to):
  • Information Technology/Decision Support
  • Senior Administrators
  • Patient safety leads
  • Nursing staff

Antimicrobial Stewardship Program: Importance of an ASP Champion

• ASP champions are typically a physician and/or pharmacist

• ASP success is critically dependent on the ASP champion(s)
  • Relationships and credibility are key: an ASP with all the right ‘pieces’ will fail if the champion is not a respected and credible individual
Antimicrobial Stewardship Program: Importance of an ASP Champion

• PHO interviewed hospitals in Ontario with existing ASPs and the following qualities were identified as important in ASP champions:
  • Believes in and is dedicated to improving patient quality of care through ASPs
  • Approachable
  • Respected by their peers
  • Perceived as a confident leader
  • Good interpersonal skills
  • Team player
Antimicrobial Stewardship Program: The Components

- Examples of ASP components:
  - Prospective audit with intervention and feedback
  - Formulary restriction and preauthorization
  - Education
  - Guidelines and clinical pathways
  - Antimicrobial order forms
  - Streamlining and de-escalation of therapy
  - Dose optimization
  - Parenteral to oral conversion

- Each ASP needs to determine which components will work in their hospital
- Components within an ASP may change over time

Metrics and Evaluations

• Measuring the impact of an ASP is an essential component of an ASP

• No consensus as to the optimal measurement strategy

• Examples of ASP measurement options include:
  • Defined daily dose (DDD)
  • Days of therapy (DOT)
  • Length of therapy (LOT)
  • Antimicrobial trends
  • *Clostridium difficile* rates
  • Antimicrobial expenditures
  • Grams of antimicrobials
  • If doing prospective audit and feedback: proportion of interventions accepted

See PHO Metrics and Evaluation Module for additional details on choosing ASP measurements
Metrics and Evaluation Bottom Line:

- Measure something
- Measure what you can, reliably and consistently
- Essential to use the metrics to evaluate the ASP on an ongoing basis and share results with stakeholders in the organization
ASP Education and Awareness

• ASP team members must feel adequately educated about ASPs and/or have a strategy to acquire further training:
  • Job shadowing
  • Workshops/conferences/on-line training
  • Communities of practice

• A communication strategy to other health care workers regarding ASP initiation is helpful when starting an ASP

• Ongoing staff education about ASPs by ASP team members is useful

• Communication strategy for disseminating ongoing ASP initiatives is typically also needed
Antimicrobial Stewardship: The Evidence (Selected examples)

<table>
<thead>
<tr>
<th>Study, year, design</th>
<th>Location</th>
<th>Type of ASP Introduced</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elligsen et al 2012</td>
<td>University teaching hospital, Toronto, ON</td>
<td>Audit and feedback in Critical Care Units from: -3&lt;sup&gt;rd&lt;/sup&gt; gen cephalosporins -β-lactam/β-lactamase inhibitors -Carbapenems -Fluoroquinolones -Vancomycin</td>
<td>-Days of therapy -AROs -C. difficile -Length of stay -ICU mortality</td>
</tr>
</tbody>
</table>

AROs: Antimicrobial resistant organisms

Monthly use of broad-spectrum antibiotics in critical care patients and control medical and surgical ward patients

© University of Chicago Press, 2012. Adapted with permission.


www.oahpp.ca
Overall susceptibility of gram-negative bacteria isolated from intensive care unit patients during the pre-intervention period versus during the post-intervention period


www.oahpp.ca
# Antimicrobial Stewardship: The Evidence (Selected examples)

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<tbody>
<tr>
<td>Leung et al 2011 Before/After Study</td>
<td>Community Hospital, Toronto, ON</td>
<td>Audit and Feedback</td>
<td>Cost and DDD - C. difficile</td>
</tr>
</tbody>
</table>

DDD: Defined Daily Dose

Can J Hosp Pharm 2011;64(5):314–320
Prospective Audit and Feedback Model

**Figure 1.** Prospective audit and feedback model within an antimicrobial stewardship program (ASP). ICU = intensive care unit, ID = infectious diseases.
Comparison of Antimicrobial Costs in the ICU Before and After Implementation of Prospective Audit and Feedback

<table>
<thead>
<tr>
<th>Period</th>
<th>Total Cost</th>
<th>Patient-Days</th>
<th>Mean Cost per Patient-Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>April to June 2009 (baseline period)</td>
<td>$58,544</td>
<td>1373</td>
<td>$42.63</td>
</tr>
<tr>
<td>April to June 2010 (pilot period)</td>
<td>$30,627</td>
<td>1127</td>
<td>$27.18</td>
</tr>
<tr>
<td>July to September 2010 (post-pilot period)</td>
<td>$22,010</td>
<td>1202</td>
<td>$18.31</td>
</tr>
</tbody>
</table>

Can J Hosp Pharm 2011;64(5):314–320
Comparison of Utilization of Broad-Spectrum and Antipseudomonal Antimicrobials

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Baseline Period</th>
<th>Pilot Phase</th>
<th>Post-Pilot</th>
<th>p value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime§</td>
<td>0.89</td>
<td>0.60</td>
<td>0.67</td>
<td>0.56</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>10.26</td>
<td>5.38</td>
<td>10.86</td>
<td>0.37</td>
</tr>
<tr>
<td>Ciprofloxacin§</td>
<td>10.44</td>
<td>10.82</td>
<td>7.67</td>
<td>0.24</td>
</tr>
<tr>
<td>Gentamicin§</td>
<td>3.97</td>
<td>1.61</td>
<td>0.29</td>
<td>0.012</td>
</tr>
<tr>
<td>Meropenem§</td>
<td>11.38</td>
<td>7.46</td>
<td>5.78</td>
<td>0.030</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>8.47</td>
<td>3.92</td>
<td>4.74</td>
<td>0.012</td>
</tr>
<tr>
<td>Piperacillin–tazobactam§</td>
<td>25.63</td>
<td>12.45</td>
<td>12.19</td>
<td>0.004</td>
</tr>
<tr>
<td>Tobramycin§</td>
<td>0.58</td>
<td>0.28</td>
<td>1.87</td>
<td>0.70</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0</td>
<td>0.75</td>
<td>0</td>
<td>0.36</td>
</tr>
<tr>
<td>All antipseudomonal antimicrobials</td>
<td>63.16</td>
<td>38.59</td>
<td>28.47</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Baseline period = April to June 2009, pilot phase = April to June 2010, post-pilot phase = July to September 2010.
†Defined daily doses per 100 patient-days, a standard measure of doses administered, developed by the World Health Organization.
‡For comparison between baseline (April to June 2009) and post-implementation period (April to September 2010).
§Agent with antipseudomonal activity.

Can J Hosp Pharm 2011;64(5):314–320
Antimicrobial Stewardship: The Evidence (Selected examples)

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<tr>
<td>Carling et al 2003</td>
<td>University-affiliated community teaching hospital, Boston, MA</td>
<td>Audit and feedback from: -3rd gen cephalosporins -Aztreonam -IV fluoroquinolones -Imipenem</td>
<td>-Antimicrobial use -C. difficile -AROs -Costs</td>
</tr>
</tbody>
</table>

AROs: Antimicrobial resistant organisms

IV antibiotic use, cost per 1,000 patient days and medicare case mix index (MCCMI) trends following implementation of the ASP.


Rates of nosocomial *C. difficile* (Top) and resistant Enterobacteriaceae infections (Bottom), before and after implementation of the ASP


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<tr>
<td>Gross R et al 2001</td>
<td>University teaching hospital, Philadelphia, PA</td>
<td>Audit and feedback and Prior authorization</td>
<td>-Appropriate antibiotic selection -Clinical cure rates -Clinical failure rates -AROs</td>
</tr>
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AROs: antimicrobial resistant organism

Clinical outcomes in a randomized controlled trial comparing the Hospital of the University of Pennsylvania’s ASP to usual practice

## Antimicrobial Stewardship: The Evidence (Selected examples)

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<tr>
<td>Valiquette et al 2007</td>
<td>Secondary/tertiary care hospital, Quebec, Canada</td>
<td>Audit and feedback: -2&lt;sup&gt;nd&lt;/sup&gt; gen cephalosporins -3&lt;sup&gt;rd&lt;/sup&gt; gen cephalosporins -Ciprofloxacin -Clindamycin -Macrolides</td>
<td>-Total antimicrobial use -Targeted antimicrobial use -C. difficile rates</td>
</tr>
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Targeted antibiotic consumption and nosocomial *C. difficile* incidence per 1000 patient-days of hospitalization

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<td>Standiford et al 2012</td>
<td>Tertiary care hospital, Baltimore, Maryland</td>
<td>Pre-authorization of antimicrobials and Guidelines</td>
<td>Costs</td>
</tr>
</tbody>
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<td>Cisneros et al 2013</td>
<td>University teaching hospital, Seville Spain</td>
<td>Counselling interviews (one-on-one educational program)</td>
<td>Appropriateness of antimicrobial Rxs, DDD, Cost, Satisfaction survey</td>
</tr>
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Clin Microbiol Infect 2014; 20: 82–88
Rates of Inappropriate Antimicrobial Use During the First Year

Clin Microbiol Infect 2014; 20: 82–88
Evolution of the Consumption by Class of Antimicrobial During the First Year

Clin Microbiol Infect 2014; 20: 82–88
Overall Healthcare Associated (HA)-MRSA rates, CNISP 1995-2011
(per 1,000 patient-admissions)

© Public Health Agency of Canada
Source: Canadian Nosocomial Infection Surveillance Program (CNISP), Public Health Agency of Canada. 2011.
Choosing Where to Start: Pick the Low Hanging Fruit

• Select the most obtainable targets for early successes
  • Select the ‘low hanging fruit’

• Examples of less effort-intensive resources include:
  • IV to PO conversion programs
  • Therapeutic substitutions
  • Formulary restrictions
  • Prospective audit and feedback on a specific antimicrobial agent or prospective audit and feedback on a specific clinical syndrome

Prospective Audit and Feedback for a Clinical Syndrome: Urinary Tract Infections

• Antibiotic use is common in setting of asymptomatic bacteriuria, despite guidelines stating that antibiotics are almost never needed for this indication

• Broad spectrum antibiotics are commonly used (i.e. ciprofloxacin)

• Ideal clinical syndrome for an ASP intervention

• The following slides outline ‘real world’ examples of how two Ontario hospitals focused on reduction of antimicrobial therapy for asymptomatic bacteriuria as part of their ASP

Lakeridge Hospital –
Whitby Rehabilitation Unit, Oshawa
Intervention

1. Education of rehabilitation unit staff
   • Signs/symptoms warranting urine culture
   • Management of asymptomatic bacteriuria/UTIs in the chronic care setting
   • Harm reduction through use of narrow spectrum/less C. difficile-prone antibiotics

2. Audit and Feedback
   • ASP pharmacist to Nurse Practitioner(s)
   • Weekly to twice weekly by phone

• Results
  • Significant reduction in overall and targeted antimicrobial
  • Only 1 new hospital acquired C. difficile case since initiation of intervention (~7 months)
St. Joseph's Healthcare, Hamilton

• Audit of urine cultures over 1 month:
  • 67 positive culture were reviewed
  • 39/67 (58%) were treated with antibiotics
  • 11/67 (16%) were symptomatic
  • Therefore, 28/67 (42%) were asymptomatic but treated with antibiotics

• Interventions
  • Education of physicians, nurses and trainees
  • Provision of laminated cards detailing management of asymptomatic bacteria
  • Daily antibiotic review rounds with physician and pharmacist (prospective audit and feedback)
ASP Getting Started: Summary and Conclusions

1. Work with those who want to work with you – start small and spread
2. Be flexible – what works in one place may or may not work in another. No one size fits all
3. Engage those you want to change – what would work for them?
4. Education is necessary but not sufficient
5. Success can be achieved without having subspecialty MDs (ID, Micro) on staff
6. Don’t use lack of technology or databases as a crutch not to improve.
   • Improvement can happen in the absence of technology
7. Measure what you can
8. Work within your existing culture and workflow
9. Harm reduction (i.e. switching antibiotics) is good too
10. Celebrate your successes and communicate these clearly

• Canadian Nosocomial Infection Surveillance Program (CNISP), Public Health Agency of Canada. Results of the surveillance of methicillin resistant *staphylococcus aureus*, from 1995 to 2009. Ottawa, ON: Her Majesty the Queen in Right of Canada; 2011. Figure 1A, Overall MRSA rates, CNISP 1995-2009 (per 1,000 patient admissions); p.4 Available from: [http://www.phac-aspc.gc.ca/nois-sinp/projects/res2009/index-eng.php#f1a](http://www.phac-aspc.gc.ca/nois-sinp/projects/res2009/index-eng.php#f1a)


Ohl CA, Dodds Ashley ES. Antimicrobial stewardship programs in community hospitals: the evidence base and case studies. Clin Infect Dis. 2011;53(suppl 1):S23-S28. Figure 1. Clinical outcomes in a randomized controlled trial comparing the Hospital of the University of Pennsylvania’s antimicrobial stewardship program (ASP) to usual practice; p. s24.
References:

• Patrick DM, Hutchinson, J. Antibiotic use and population ecology: how you can reduce your “resistance footprint”. CMAJ 2009;180(4):416-421. Figure 1, Fluoroquinolone use and correlation to ciprofloxacin resistance among uropathogens in British Columbia; p. 417.


• Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33(4):322-7

• Standiford HC, Chan S, Tripoli M, Weekes E, Forrest GN. Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. Infect Control Hosp Epidemiol. 2012;33(4):338-45


• Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental prevalence study. Lancet Infect Dis. 2011;11(5):355-62. Figure 1, Map of NDM-1 positive samples from New Delhi centre and surrounding areas; p. 357
References:
