Antimicrobial Stewardship: Why, When, Where and How?

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Canadian Antimicrobial Resistance Alliance (CARA)

Antimicrobial Resistant Infections

- Surveillance/epidemiology
- Rapid Diagnostics
- Mechanisms
- Treatment/Prevention

Patient outcomes
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Objectives

1. Understand the **benefits** of an antimicrobial stewardship program

2. Realize how **easy** it is to start or upgrade your antimicrobial stewardship program

3. Be aware of the various antimicrobial stewardship program **interventions**
Question #1

What is 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**

What is an Antimicrobial Stewardship Program (ASP)?

Specific program and interventions to monitor and direct antimicrobial use at a health care institution, thus providing a standard evidence-based approach to judicious antimicrobial use.
Question #2

Why Care About Antimicrobial Stewardship?
Why Care About Antimicrobial Stewardship?

- Up to 50% of antimicrobial use in hospitals is inappropriate

- 77% (51/66) studies of interventions to improve antimicrobial use in hospitals had beneficial results
Potential **Benefits** of Antimicrobial Stewardship

1. **Reduce antibiotic resistance**
   (e.g. 3rd Gen Cephalosporins and Enterobacter resistance)

2. **Reduce drug-related adverse events**
   (e.g. excessive antibiotic exposure and *C. difficile*)

3. **Improve clinical outcomes**
   (e.g. optimizing PK and PD)

4. **Reduce health care costs**

Antimicrobial Stewardship in the 1980’s (Goal - Reduce Costs)

Prospective audit with intervention and feedback:

- **Issue**: Obs/Gyn using cefoxitin for vag/abd hysterectomy and C-sections (published guidelines said cefazolin)
- **Effect of intervention** on prescribing antimicrobials for prophylaxis in Obs/Gyn surgery (1100 tertiary bed hospital in Winnipeg)
- **Pre-intervention audit**: Jan – March 1987, 32% (39/123) used cefazolin
Antimicrobial Stewardship in the 1980’s (Goal - Reduce Costs)

- **Intervention and feedback:** May-July 1987, letter describing the findings of audit as well as Obs/Gyn surgery prophylaxis guidelines to Obs/Gyn. Sept 1987 Obs/Gyn section adopts guidelines and changes practice

- **Post-intervention:** Sept - Nov 1988, 93% (98/105) used cefazolin

- **Outcome:** Annual savings ~$25,000
Resistance Perception

Antimicrobial Stewardship Project

If antimicrobial resistance is a problem, then where? (By hospital type)

- Academic HSC (n=27)
- Non-Academic HSC (n=86)

- A problem in your hospital: 92% (Academic), 65% (Non-Academic)
- A problem in Ontario: 96% (Academic), 94% (Non-Academic)
- A problem in Canada: 92% (Academic), 93% (Non-Academic)
- A problem in other parts of the world: 96% (Academic), 83% (Non-Academic)
Why are Antibiotic Resistant Infections Important to Infectious Diseases

- Greater morbidity and mortality
- Hospitalization and supportive care
- Increased use of:  
  - Laboratory and diagnostic tests  
  - Infection control procedures  
  - More expensive antimicrobials  
  - Length of hospital stay and lost work days

New systemic antibacterial agents approved by the US FDA

Boucher et al. CID 2013;56(12):1685-1694.
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)
   - Minimize unnecessary antimicrobial use
   - Targeted (narrow spectrum) therapy

3. Continued discovery of new antimicrobials

4. Reduce resistance reservoirs (i.e. animal/environmental use)

5. Antimicrobial stewardship programs

Question #3

What Are the Goals of Antimicrobial Stewardship In 2013?
Potential Benefits of Antimicrobial Stewardship

1. Reduce antibiotic resistance (e.g. 3rd Gen Cephalosporins and Enterobacter resistance)

2. Reduce drug-related adverse events (e.g. excessive antibiotic exposure and C. difficile)

3. Improve clinical outcomes (e.g. optimizing PK and PD)

4. Reduce health care costs

Antimicrobial Stewardship Program (ASP)

NUTS AND BOLTS
- How
- Who
How do you start or upgrade ???

- Create a **business case** that is not solely based on saving money
- ID specialist and Director of Pharmacy
- Be on the lookout for **opportunities** to levy support/resources
  - Nosocomial infection outbreaks
  - Institution priority on patient-safety
  - Accreditation

Antimicrobial Stewardship Program (ASP) Team

- ASP CORE members should include (not limited to):

  - ID Physician
    - Needs to be the **stewardship champion**
  - Pharmacist
    - Ideally has ID training (formal or informal)
  - Clinical microbiology
  - Infection prevention and control
  - Informational system specialist
  - Hospital epidemiologist

Many different interventions have been successful:

- **No direct comparisons** of interventions, therefore difficult to determine the most effective ones

- **Resources required** to implement such interventions and programs are not well described
Antimicrobial Stewardship Program (ASP)

- No ‘one size fits all’
- ASPs should be tailored to each hospital and depends on:
  - **Resources**
  - Hospital size
  - Local antimicrobial use/resistance patterns
  - Patient population

Examples of ASP strategies/interventions:

- Education
- Formulary
- Formulary restriction and preauthorization
- Selective reporting
- Prospective audit with intervention and feedback
- Guidelines and clinical pathways
- Antimicrobial order forms
- Streamlining and de-escalation of therapy
- Dose optimization (optimize PK/PD)
- Parenteral to oral conversion

Examples of ASP strategies/interventions:

Education

- Essential
- Alone, not sufficient (B-II)
- No sustained impact
- Education + intervention (A-III)

Examples of ASP strategies/interventions:

Formulary (A-II)

- proven and widely adopted
- eg. 3rd/4th gen Cephs

Examples of ASP strategies/interventions:

Formulary restriction and preauthorization (A-II, B-II)

- eg. Restrict to ID (eg. meropenem, daptomycin)
- ? Mandatory ID phone call/approval ?
- ? Mandatory ID consult

Examples of ASP strategies/interventions:

Selective reporting (Clinical Microbiology) [A-III]

- Blood/Urine E. coli
  - Susceptible to Ampicillin
  - Susceptible to Cefazolin

Examples of ASP strategies/interventions:

Prospective audit with intervention and feedback (A-I)

- Very effective
- Resource intensive

Examples of ASP strategies/interventions:

Guidelines and clinical pathways (A-I – A-III)

- eg. CAP pathway
- National guidelines made local
- Very effective

- Guidelines (tough for section to adopt)

Examples of ASP strategies/interventions:

Antimicrobial order forms (B-II)

- Many types
- Can be effective (reinforce guidelines)
- Need detail, no shortcuts

Examples of ASP strategies/interventions:

- Streamlining and de-escalation of therapy A-II
  - Severe infections in ICU
  - Very effective with ASP

Treatment and De-escalation in Severe Infection

- Empiric broad spectrum treatment-ASAP
- Culture
- **3 days ASP re-evaluation:**
  - Cultures
  - Clinical improvement
- De-escalation:
  - 1 agent: change to narrow spectrum agent
  - 2 agents: change to 1 agent

Examples of ASP strategies/interventions:

Dose optimization (A-II)

Optimize PK/PD

- T/MIC for β-lactams

- AUC/MIC and Cmax/MIC for FQ and aminoglycosides

Pharmacodynamic Principles for Beta-Lactams

• The time drug concentration exceeds the MIC (T>MIC) is predictive of antibacterial effect

• Methods to Increase % Time > MIC
  - Higher doses
  - More frequent dosing
Limited improvement in target attainment by increasing to highest recommended doses

Zelenitsky and Zhanel. JAC 2011.
Optimizing β-lactam Therapy: Maximizing Percent T>MIC

Other dosing strategies to improve T> MIC

• Increased duration of infusion
  - Continuous infusion
    » Administer loading dose, then use pump to give total daily dose IV over 24 hr period

  - Prolonged infusion
    » Same dose and dosing interval, however, change duration of infusion (0.5 hr → 3 - 4hr)
Significant benefit in target attainment for piperacillin-tazobactam by using prolonged infusions

Zelenitsky and Zhanel. JAC 2011.
Extended-Infusion Dosing Strategy: Piperacillin / Tazobactam for P aeruginosa Infection

- Retrospective cohort study
- Extended (4 h) vs. intermittent (30 min) infusion
- Infusion schedule not associated with differences in mortality or length of stay for patients with APACHE II score <17

Patients With APACHE II Score e17

- 14-Day Mortality
  - Extended infusion: 12.2%
  - Intermittent infusion: 31.6%
  - P = 0.04

- Length of Stay (d)
  - Extended infusion: 21
  - Intermittent infusion: 38
  - P = 0.02

Examples of ASP strategies/interventions:

Parenteral to oral conversion (A-III)

- High F%
- Fluoroquinolones
- TMP/SMX
- Metronidazole
- Clindamycin
- Linezolid
- Minocycline
- Fluconazole
- Voriconazole
- Chloramphenicol
Measure What You Can

**Metrics and Evaluations:**
- 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:
  - % of interventions accepted

Comparative antibiotic utilization from 2005 to 2011.
Our VAP Infection Rates
Clinical examples that they work
Antimicrobial Stewardship Program (ASP) Evidence

- **Location**: Tertiary care hospital Quebec

- **ASP**: Audit and feedback
  - 2\textsuperscript{nd}/3\textsuperscript{rd} Gen Cephs
  - Ciprofloxacin
  - Clindamycin
  - Macrolides

- **Outcomes**
  - Total AB use/targeted AB use
  - C. difficile rates

Antimicrobial Stewardship Program (ASP) Evidence

Antimicrobial Stewardship Program (ASP) Evidence

- **Location**: Univ teaching hospital Toronto

- **ASP**: Audit and feedback in critical care units
  - $3^{rd}$ Gen Cephs
  - ’-lactam/’-lactamase inhibitors
  - Carbapenems
  - Fluoroquinolones
  - Vancomycin

- **Outcomes**
  - Days of therapy
  - Length of stay
  - ICU mortality
  - Resistance rates
  - *C. difficile*

Antimicrobial Stewardship Program (ASP) Evidence

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

Antimicrobial Stewardship Program (ASP) Evidence


GNB susceptibility in ICU
Antimicrobial Stewardship Program (ASP) Evidence

- **Location**: Univ teaching hospital Philadelphia
- **ASP**: Audit and feedback and prior authorization
- **Outcomes**
  - Appropriate antibiotic selection
  - Clinical cure rates
  - Clinical failure rates
  - Resistance rates

Antimicrobial Stewardship Program (ASP) Evidence

Outcomes in a randomized controlled trial comparing the University of Pennsylvania Hospital ASP to usual practice

- Antimicrobial Appropriate
- Cure
- Failure
- Resistance

Antimicrobial Stewardship and Carbapenems

- Group 1 - ertapenem
- Group 2 - imipenem, meropenem, doripenem

Questions:
- When to use Gp 1 vs Gp 2
- Does ertapenem use drive resistance to imip/merop
Ertapenem (Gp 1) vs. Imipenem and Meropenem (Gp 2)

• Broad-spectrum:
  - Similar activity to imipenem/meropenem versus...
    • Gram-positive cocci
    • Gram-negative bacilli
    • Anaerobes
  - Less activity to imipenem/meropenem versus...
    • Enterococcus spp., P. aeruginosa and Acinetobacter spp.

Mean Carbapenem Use and Pseudomonas aeruginosa Susceptibility at 25 Hospitals during the 9 Years Surrounding Adoption of Ertapenem

- No relationship found between rate of ertapenem use and change in Pseudomonas aeruginosa carbapenem susceptibility over 9 years

Antimicrobial Stewardship Program (ASP)

Where to start?

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 A-III
- Formulary restrictions A-II, B-II
- Prospective audit and feedback on a specific antimicrobial or a specific clinical syndrome A-I
- Guidelines and clinical pathways (A-I – A-III)

ASp Conclusions

1. Need a champion
2. Need new resources
3. Start small then spread
4. Engage those you want to change
5. Education is necessary but not sufficient
6. Don’t use lack of technology or databases as a crutch not to improve
7. Measure what you can
8. Work within your existing culture/ workflow
9. Celebrate your successes and communicate these clearly
Ideal Antimicrobial Stewardship Program

- ID physician champion
- ID pharmacist
- Committed CORE ASP team
- Collaboration ASP/IC/PT
- Medical administration support
- Medical staff support
- Multipronged ASP
  - various interventions
  - ongoing audit/intervention/feedback
- Measured outcomes
Antimicrobial Stewardship