Antibiotic Challenge

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Dalhousie Academic Detailing Service
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Disclosure

Isobel Fleming has no actual or potential conflict of interest with this topic or presentation.

Edith Baxter has no actual or potential conflict of interest in relation to this topic or presentation.
OBJECTIVES:

With the guidance of antibiotic stewardship, use cases to consider appropriate therapy for infections of the:

1. Respiratory Tract
2. Urinary Tract
3. Skin and soft tissue.
ABX: LIFESAVING When Used Correctly...

- In 2016, an estimated 22.6 million Rx were dispensed in Canada, with a total expenditure of nearly $700 million.
  - ≥ 30% of these Rx were likely inappropriate.

- Misuse of Antibiotics has led to global crisis of antimicrobial resistance.

- Identify and stop inappropriate antibiotics use to slow emergence of antimicrobial-resistant microorganisms & minimize collateral damage.
Collateral Damage

• Patients taking broad spectrum Antibiotics are up to 3x more likely to get another infection from an even more resistant pathogen.

• Up to 20% experience adverse events:

<table>
<thead>
<tr>
<th>GI complications</th>
<th>Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered microbiome</td>
<td>Renal injury</td>
</tr>
<tr>
<td>Hematologic side effects</td>
<td>Hepatobiliary effects</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>QT prolongation</td>
</tr>
</tbody>
</table>

• Financial burden
Antimicrobial Stewardship

- Maximize clinical success of antibiotics

- Minimize unintended consequences of their use
  - Antimicrobial resistance
  - Adverse events
Principles of Antimicrobial Stewardship

- Antibiotics only when indicated
- Consider delayed Rx
- Select most appropriate antibiotic
  - Older > newer
  - Reserve Fluoroquinolones
  - Consider recent Antibiotic use
- Use the proper dose and duration
Principles of Antimicrobial Stewardship

• Avoid mislabeling adverse effects as allergies
• Treat for the shortest effective duration
• Understand the patient’s risk factors for infection with a resistant bug
  • Antibiotic use in past 3 months
  • Exposure to children in daycare
  • Recent travel/immigration from areas with high rates of AMR
  • Exposure to healthcare facilities
Antibiotic Stewardship Programs & Resources

Canadian (continued)

- Waiting room poster stating a commitment to not treat viral infections with antibiotics

- National Collaborating Centre for Infectious Diseases (NCCID)
  - Viral Rx pads and communication materials
    - [https://nccid.ca/antibiotic-awareness/](https://nccid.ca/antibiotic-awareness/)

- Choosing Wisely Canada
  - [https://choosingwiselycanada.org/campaign/antibiotics/](https://choosingwiselycanada.org/campaign/antibiotics/)
Antimicrobial Treatment Guidelines for Common Infections

March 2019

Published by:
The NB Provincial Health Authorities Anti-infective Stewardship Committee under the direction of the Drugs and Therapeutics Committee
Outpatients - Gram Positive Isolates: % Susceptible (Oct 2016- Sept 2017)

<table>
<thead>
<tr>
<th></th>
<th>Amoxicillin/Clavulanate</th>
<th>Ampicillin</th>
<th>Penicillin</th>
<th>Cloxacillin</th>
<th>Ceftriaxone</th>
<th>Clindamycin</th>
<th>Erythromycin</th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Nitrofurantoin</th>
<th>SXT/TMP</th>
<th>Doxycycline</th>
<th>Vancomycin</th>
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<tbody>
<tr>
<td>Staphylococcus aureus</td>
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<td>88</td>
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<td>72</td>
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<td>MRSA</td>
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<td>Coagulase negative</td>
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<td>Staphylococcus</td>
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</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>240</td>
<td>99<strong>b</strong></td>
<td>99<strong>b</strong></td>
<td>-</td>
<td>-</td>
<td><strong>R</strong></td>
<td><strong>R</strong></td>
<td><strong>R</strong></td>
<td><strong>R</strong></td>
<td>98</td>
<td><strong>R</strong></td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>63</td>
<td>10<strong>c</strong></td>
<td>10<strong>c</strong></td>
<td>10<strong>c</strong></td>
<td>10<strong>c</strong></td>
<td>84</td>
<td>84</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
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<tr>
<td>Streptococcus pyogenes</td>
<td>38</td>
<td>100<strong>d</strong></td>
<td>100<strong>d</strong></td>
<td>100<strong>d</strong></td>
<td>100<strong>d</strong></td>
<td>84</td>
<td>84</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td><strong>R</strong></td>
<td>-</td>
<td>100<strong>d</strong></td>
</tr>
<tr>
<td>Group A Streptococcus</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Streptococcus pneumoniae</td>
<td>64</td>
<td>69<strong>e</strong></td>
<td>69<strong>e</strong></td>
<td>-</td>
<td>100</td>
<td>-</td>
<td>71</td>
<td>98</td>
<td>-</td>
<td>-</td>
<td>77</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

All results are rounded to the nearest whole number.

Some isolates may have duplicates included which may alter the results.

** approximate # tested as not all isolates tested against all antibiotics

* R intrinsically resistant or susceptibility < 10%

** either not tested or not active

MRSA = methicillin resistant Staphylococcus aureus

1 includes MRSA (MRSA represents approximately 12% of all S. aureus isolates)

2 inferred susceptibility from other agents

3 predicted susceptibility from literature

4 includes isolates from Oct 2014 to Sept 2016

5 non-CSF isolates (CSF isolates may have higher resistance due to lower MIC breakpoints for penicillin and ceftriaxone)

6 Doxycycline susceptibility inferred from Tetracycline

7 may be susceptible but not reported (not better than ampicillin)

8 Cefazolin and cephalixin susceptibilities can be inferred from Cloxacillin

9 for uncomplicated UTI only

10 combined inpatient and outpatient data
Principle:

• Avoid mislabelling adverse effects as allergies
β – Lactam Allergy

• Penicillin allergy is **over reported** and cross-allergy with cephalosporins is **overestimated**

• Incidence of true IgE mediated hypersensitivity to β – lactam is
  • 1 to 5 per 10,000 treatment courses for Penicillin
  • 0.1 to 100 per 100,000 for Cephalosporin

• Unnecessarily avoiding penicillin, amoxicillin & 1st gen cephalosporin can result in therapy that is:
  • less effective
  • more toxic
  • associated with greater risk of antimicrobial resistance
  • more $$
What causes β – Lactam Hypersensitivity?
**Note**

- Based on *theoretical risk*
- Studies using this approach not yet available
- Patients with history of serious non-IgE mediated reaction should **AVOID all β – lactams**

- **Document** clearly in patient health record
- **Educate** the patient
Principle

• Treat for the shortest effective duration
Short-course Antibiotic Therapy—Replacing Constantine Units With “Shorter Is Better”

Noah Wald-Dickler and Brad Spellberg
Case 1

• 68 year old male, non-smoker
• HTN, DM2, a-fib
• 2 day history of fever and cough
• Rales LLL
• T 38.5, HR 102, BP 100/56, RR 20, 02 sat 94%
Adult Community Acquired Pneumonia

• Many microorganisms cause CAP
  • *S. pneumoniae* most common
  • *H. influenzae*
  • *M. catarrhalis*
  • *P. aeruginosa*

• What about atypicals?
  • *Legionella* species, *M. pneumoniae, C. pneumoniae*
# Empiric coverage by Province:

**New Brunswick**

### CRB-65 score 0 plus O2 sat > 92% on room air

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult CAP regimen</th>
<th>Cost per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>1000 mg BID</td>
<td>$1.37</td>
</tr>
<tr>
<td>Doxycycline¹ ²</td>
<td>200 mg for 1st dose then 100 mg BID</td>
<td>$1.17</td>
</tr>
<tr>
<td>Cefuroxime²</td>
<td>500mg BID</td>
<td>$2.86</td>
</tr>
<tr>
<td>Levofloxacin³</td>
<td>750 mg once daily</td>
<td>$3.26 - $6.55</td>
</tr>
<tr>
<td>Moxifloxacin³</td>
<td>400 mg once daily</td>
<td>$1.52</td>
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*Duration of therapy is usually 5-7 days*

### CRB-65 score 1-2

Consider admission to hospital ward

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<tbody>
<tr>
<td>Amoxicillin</td>
<td>1000 mg BID</td>
<td>$1.37</td>
</tr>
<tr>
<td>Amox/Clev</td>
<td>875 mg BID</td>
<td>$1.17</td>
</tr>
<tr>
<td>Cefotaxime¹</td>
<td>1000 mg Q8H IV</td>
<td>$2.99</td>
</tr>
<tr>
<td>Ceftriaxone¹</td>
<td>1000 mg Q24H IV</td>
<td>$1.36</td>
</tr>
<tr>
<td>Levofloxacin²</td>
<td>750 mg once daily</td>
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*Duration of therapy is usually 5-7 days*

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**Nova Scotia**

<table>
<thead>
<tr>
<th>Severity</th>
<th>DS-CRB65</th>
<th>Mortality</th>
<th>Site of care</th>
<th>Empiric Therapy⁺ (start antibiotics as soon as possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>Less than 1%</td>
<td>Home (unless hospitalized for reasons other than pneumonia)</td>
<td>amoxicillin 1000 mg PO q8h + doxycycline 100 mg PO q12h or amoxicillin-clavulinate 875/125 mg PO q12h or cefuroxime axetil 600 mg PO q8h (if true immediate penicillin allergy)</td>
</tr>
</tbody>
</table>
| Moderate | 2-3      | 3-4%      | Hospital     | amoxicillin 2 g IV q6h + [doxycycline 100 mg PO q12h OR Macrolide PO (see comments) OR azithromycin 500 mg IV q24h x 3 days, then STOP] or cefuroxime 1.5 g IV q8h + [doxycycline 100 mg PO q12h or Macrolide PO (see comments) OR azithromycin 500 mg IV q24h x 3 days, then STOP]
Beta-lactam plus macrolides or beta-lactam alone for CAP: A systematic review and meta-analysis

Respirology (2016)21,1193-2000

• Does one strategy lead to better survival?

• 14 trials → 12 observational studies, 2 open label RCTs, 1 non RCT interventional study → N= 33 332

• Severity → PSI < III, CURB-65 or CRB-65 < 1 MILD/MODERATE → PSI > IV, CURB-65 or CRB-65 > 2 SEVERE

• Primary outcome: 90 day mortality
Theoretical considerations for beta-lactam plus macrolide

1. Atypical coverage by macrolide

2. Synergism between beta-lactam and macrolide

3. Anti-inflammatory effect of macrolide
Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

- Cluster randomized, crossover, non-inferiority, pragmatic trial in the Netherlands
- Beta-lactam vs beta-lactam plus macrolide or fluoroquinolone in adults with CAP
  - Sample size of at least 650 per arm
- Hospital based study, median CURB-65 score of 1, median age 70
- Study used “treatment strategies” as opposed to individual antibiotics
- Primary endpoint → 90 day mortality
- **Bottom line:** beta-lactam monotherapy was non-inferior to beta-lactam + macrolide
CAP-START trial

• Limitations and Uncertainties:
  • Beta-lactam arm had up to 38% who also received atypical coverage
  • Dose and duration of antibiotics were not provided
  • Hospitalized patients, standard of care and pathogens in the Netherlands may not be generalizable to Canada

• Empirical atypical coverage was reduced by 67% during the beta-lactam strategy periods vs. beta-lactam+macrolide strategy periods and by 69% during the beta-lactam strategy periods as compared with the fluoroquinolone strategy periods
Adult Community Acquired Pneumonia

- Amoxicillin susceptibility is MUCH higher than reported in local antibiogram in NSHA
- Amoxicillin 1000 mg bid reasonable first choice for CAP treatment as outpatient

Outpatients - Gram Positive Isolates: % Susceptible (Oct 2016- Sept 2017)

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<td>76</td>
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</table>
Adult Community Acquired Pneumonia

• Cefuroxime (500 mg bid) and Doxycycline (200 mg x1, then 100 mg bid) reasonable alternatives for outpatient treatment

• Consider Levofloxacin and Moxifloxacin:
  • Outpatients failing Amoxicillin
  • Inpatients (hospital ward) if beta-lactam contraindicated

• Duration 5-7 days
Case 2

• 3 year old
• Fever, irritability for 48 hr
• Older sibling with strep pharyngitis
• Initial swab → RADT negative, culture positive

• Feels fine when you call parents with swab results

• Do you treat?
• Which antibiotic?
• Dose and interval?
Causes of pharyngitis in kids

• >70% viral

• Bacterial:
  • *Strep pyogenes*
  • Group C and G *Streptococci*
  • *A. hemolyticum*
  • *Mycoplasma* and *Chlamydia* species
  • *N gonorrhoeae*
  • *C. diphtheria*
Group A Streptococcus

- GAS pharyngitis is typically **self limited**

- Antimicrobials decrease severity of symptoms and duration by **ONE** day

**Complications of GAS**

- **Suppurative**
  - epiglottitis
  - peritonsillar abscess
  - retropharyngeal abscess

- **Non-suppurative**
  - Rheumatic fever
  - Post streptococcal glomerulonephritis
Risk of rheumatic fever?

• Prevalence difficult to estimate 0.1-2 cases per 100,000

• Higher in remote and Aboriginal communities 8.33 per 100,000

• One estimate “…it took 12 General Practitioners’ working lifetimes to encounter one new case of acute rheumatic fever in Western Scotland in the 1980s.”

  *Journal of the Royal College of General Practitioners 1985;35:223-4*

• IDSA, ACP, AAP → recommend treatment to prevent complications
  → initiate within 9 days of onset of infection
Treatment

• Pen V 25-50 mg/kg/day divided TID or QID (max 3000 mg/day)
  • Older child or adolescent 300-600 mg BID- TID

• Amoxicillin 50 mg/kg/day divided OD, BID or TID
  • Evidence: 1 RCT, investigator blinded, non-inferiority trial (N=652)
    Amoxicillin (750 or 1000mg) OD vs. Amoxil (375 or 500 mg) BID
    No statistically significant difference in bacteriologic failure rates
    Pediatr Infect Dis J 2006;25:761-7
If previous allergy to Amoxicillin

- Cefuroxime 20 mg/kg/day divided BID

- Clarithromycin 15 mg/kg/day divided BID
  - Increasing rates of GAS resistance to macrolides
**Otitis media, Sinusitis and Pneumonia in kids**

**Acute Otitis Media**
- Low dose amoxicillin (45-60 mg/kg) **TID**
- High dose amoxicillin (75-90 mg/kg) **BID**
- Both regimens provide adequate middle ear concentrations for >50% of the day

**Acute bacterial sinusitis**
- No trial evidence to support dosing interval
- Local experts recommend **TID** amoxicillin
- Max 3000 mg/day

**Uncomplicated pneumonia**
- Amoxicillin 40-90 mg/kg **TID**
- Max 4000 mg/day

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**5 or 10 days, depending on age**

**10-14 days**

**7-10 days**
Case 3

- 75 year old female
- Symptoms that “feel like previous UTI”

- Urine cloudy, foul smelling x 2 months
- Some urgency, denies dysuria or ↑ frequency
- Afebrile, vitals stable

- Past history of HTN, CRF → CrCl 45
- Sulfa allergy
Diagnosis of Suspected Urinary tract Infection (UTI) in Non-Catheterized Elderly Patients in Acute Care Setting

**PRACTICE POINTS:**
- UTI is a clinical diagnosis, not a laboratory diagnosis
- Dipsticks not recommended – poor diagnostic accuracy
- Urinalysis:
  - Presence of bacteria/nitrites and/or WBC not diagnostic of UTI as common finding in the elderly
  - Absence of WBCs in urine rules out UTI
- Do not start antibiotics before urine sample collected
  - ≥ 3 organisms typically implies contamination

**TYPICAL URINARY TRACT INFECTION SIGNS/SYMPTOMS:**
- Acute dysuria and/or
- 2 or more of the following:
  - Fever
  - New urgency (or marked increase)
  - New frequency (or marked increase)
  - Suprapubic/flank pain
  - New urinary incontinence
  - Cross infection

**Hemodynamic instability and/or mental status change**
- Contact healthcare provider for urgent management

**NO**
- Leukocyte esterase negative/trace/small or WBC < 5/hpf
  - Urine culture Note: For female patient, strongly recommend n/catheter urine culture
    - No pathogens reported
      - UTI unlikely
        - Consider alternative diagnosis
        - Rehydrate/push fluids (up to 1L) for 24hrs.
        - Reassess clinical condition
    - ≥ 3 organisms or reported as mixed contaminated
      - Contact healthcare provider if fever and/or flank pain
        - Repeat with in/out catheter urine
        - Rehydrate/push fluids (up to 1L) for 24hrs.
      - Treat for UTI
    - 1 or 2 uropathogens with susceptibility results

**YES**
- Leukocyte esterase moderate/large or WBC > 5/hpf
  - Contact healthcare provider for urgent management
  - Foley catheter placement

**Hemodynamic instability and/or rapid mental status deterioration/delirium**
- Consider/assess for:
  - Dehydration
  - Drug interaction/side effects
  - Sleep disturbances
  - Sensory deprivation
  - Hypoglycemia
  - Constipation
  - Urinary retention
  - Increased falls
  - Worsening functional status
  - New/increased functional behaviour

**Cognitively functional changes**
- DO NOT ASSUME UTI
  - Consider/assess for:
    - Dehydration
    - Drug interaction/side effects
    - Sleep disturbances
    - Sensory deprivation
    - Hypoglycemia
    - Constipation
    - Urinary retention
    - Increased falls
    - Worsening functional status
    - New/increased functional behaviour

**Typically indicates dehydration**
- Rehydrate/push fluids (up to 1L) for 24hrs.
- Monitor every 6hrs.
- Reassess clinical condition.

For more directions and guidance: www.ammi.ca I #SymptomFreeLetItBe
Case 3

• What if she did have acute dysuria?

• How low is too low when it comes to renal function and avoiding the use of nitrofurantoin?

• The American Geriatrics Society 2019 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults
  • AVOID with CrCl <30 mL/min or for long term suppression
  • LOW quality evidence, STRONG recommendation

J Am Geriatr Soc 00:1-21 2019

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adult Regimen for EMPRIC Therapy</th>
<th>Cost per course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin Monohydrate/macrocysts</td>
<td>100mg BID Women 5 days: Men 7 days</td>
<td>$7.86 - $11.00</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>1 DS tab BID Women 3 days: Men 7 days</td>
<td>$0.72 - $1.68</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>500mg QID Women 5-7 days: Men 7 days</td>
<td>$9 - $12.80</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>375 mg BID Women 5-7 days: Men 7 days</td>
<td>$7.75 - $10.85</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>3 g X 1 dose (Women) 3 g every 72 hrs X 3 doses (Men)</td>
<td>$15.23 $45.69</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250 mg BID Women 3 days: Men 7 days</td>
<td>$2.67 - $6.23</td>
</tr>
</tbody>
</table>
Case 3

• 65 year old male
• Infected sebaceous cyst on back
• Minimal area of erythema, afebrile
• Type 2 diabetic, obese BMI 35
• Hospitalized for orthopedic procedure 4 months ago
• Insulin, perindopril/indapamide, rosuvastatin

• Treat or not treat?
• Dose, duration and considerations?
Skin and Soft Tissue Infections

Non-purulent

GAS

S aureus less common

Purulent

MSSA, MRSA

History of MRSA
Recent hospitalization
Injection drug use
Poor response to initial antibiotic

Mild
- No systemic signs of infection

Moderate
- Systemic signs of infection

Severe
- SIRS*
- Failed oral antibiotic therapy
- Immunocompromise
- Deep infection: bullae, skin sloughing, or end organ dysfunction
Coverage for Purulent SSTI

• **Incision and Drainage** is cornerstone of management

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Adult regimen</th>
<th>Cost per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>2g IV q8h</td>
<td>$24.00</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15mg/kg IV q12h</td>
<td>$119.32/75 kg</td>
</tr>
</tbody>
</table>

Consider adding antibiotic:
- multiple abscesses
- lack of response
- extremes of age
- Impaired host defense
Do abscesses benefit from antibiotics?

- RCT with 3 arms (n=786)
- Skin abscesses < 5 cm, after I and D
- Randomized to receive clindamycin, TMP-SMX or placebo
- Infections were 67% Staph aureas, 74% of these were MRSA
- Cure rates at 10 days:
  - Clindamycin 83%
  - TMP-SMX 82%
  - Placebo 69%
- No statistically significant difference in recurrence rates between groups
- Antibiotics can help recovery for 1 in 8 people with small, drained abscesses

Case 3- Treat as MSSA or MRSA?

- Purulent SSTI

- Cephalexin first line option

- Does obesity affect dosing for cephalexin?

- No primary evidence to support alternative dosing

- Product monograph states: “adult dosage ranges from 1 to 4 grams daily in divided doses”

- IDSA guidelines support 500 mg qid dosing
MRSA concerns

- TMP-SMX or doxycycline → diabetic patient on ACE inhibitor?
- Clindamycin may still be reasonable for CA-MRSA, national data shows higher sensitivity of MRSA to clindamycin than locally.

![Antibiotic Susceptibility Table]

**QEII Health Sciences Centre Antibiotic Susceptibility (Oct 2016- Sept 2017)- outpatients**
Summary:

• Consider shorter duration therapy when appropriate

• Amoxicillin as empiric outpatient Rx for community acquired pneumonia for adults

• Amoxicillin/Penicillin for GAS, macrolide resistance to GAS is high

• Don’t treat asymptomatic bacteriuria in older adults

• Skin and soft tissue infections: know when to consider antibiotic coverage for purulent SSTI and MRSA coverage
Antibiotic Stewardship Programs & Resources

Local
• NSHA Antimicrobial Stewardship team http://www.cdha.nshealth.ca/nsha-antimicrobial-stewardship

Canadian
• Association of Medical Microbiology & Infectious Disease (AMMI) Canada.
  • Guidance for addressing asymptomatic bacteriuria https://www.ammi.ca/?ID=127
• Bugs and Drugs (Alberta/BC) http://bugsanddrugs.ca
• Appropriateness of Care: Asymptomatic Bacteriuria https://www.albertahealthservices.ca/info/Page15718.aspx
• Sinai Health Systems-UHN Antimicrobial Stewardship Program http://www.antimicrobialstewardship.com
• Saskatchewan Health Authority Stewardship Program www.rqhealth.ca/antimicrobialstewardship
• Antibiotic Stewardship & Awareness www.RxFiles.ca/ABX