ECHO - 2018 Year in Review Highlights
Thank you all for participating with us throughout the year and for sharing your stories!
I. Fluoroquinolones and their role in treatment of UTIs - avoid if possible!

(FYI: picture copied from www.lawyersandsettlements.com)
2016 FDA Warnings: Potential fluoroquinolone side-effects

- Increased risk, greater than with most other antibiotics, for causing **C. difficile colitis**
- **Acute Tendonitis** - particularly Achilles tendonitis and rupture, can be unilateral or bilateral, and can occur **at any time** with these antibiotics
- **QT prolongation** - can cause Torsades. Some fluoroquinolones have been taken off the market because of this problem.
- **Peripheral neuropathy** - may be irreversible
- **Central nervous system toxicities** - particularly in older patients
FDA Drug Safety Communication -
FDA advises restricting use for certain uncomplicated infections. Posted May 12, 2016

- FDA recommends that:
  - 🔴 Serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections (UTI) who have other treatment options.
  - 🔵 For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.
July 2018 FDA adds additional fluoroquinolone warnings:

- **Fatal hypoglycemia**
- Report of at least 67 cases of life-threatening hypoglycemic coma- including 13 deaths, 9 with permanent and disabling injuries
- Occurred more frequently in the elderly and those with diabetes taking an oral hypoglycemic medicine or insulin.
- Others had renal insufficiency as a risk factor (Was dose renally adjusted)
- 4 of these antibiotics have labeled drug interaction already with sulfonylurea
- Seen mostly with levofloxacin (44), cipro (12)
Also, new neuropsychiatric side-effects noted in 2018 update—new labeling to make these warnings more prominent and consistent across all the fluoroquinolones.

- Disturbances in attention (new)
- Memory impairment (new)
- Delirium (new)
- Nervousness
- Agitation
- Disorientation
New approach to Asymptomatic Bacteriuria (ABU)

- Definition: **presence of bacteria >100,000 cfu/ml in urine** of an individual **without signs or symptoms of UTI**.
- This definition is **independent** of the presence or absence of pyuria, odor, cloudy urine.
Treatment of ASB just leads to drug resistant bacteria and side-effects from the antibiotic.

1. Antibiotic treatment of ASB does **not** reduce frequency of symptomatic UTIs.
2. Treatment of ASB in diabetes does **not** reduce adverse outcomes or improve glucose control.
3. It does lead to untreatable drug resistant bacteria, C. difficile infection, etc.
4. Only exceptions are pregnancy where ASB is associated with pyelonephritis, growth retardation, neonatal death... and patients undergoing urologic procedures (such as prostate bx).
Why treat Acute cystitis?

- ***Rarely*** progresses to severe disease even if untreated:
  
  goal of treatment is to ameliorate symptoms

  In selecting therapy, I. **efficacy** as well as II. “**ecologic collateral damage**” (selecting for antibiotic resistant bacteria, causing C. difficile colitis) should be considered equally-fluoroquinolones should be avoided, except in pyelonephritis

  Avoid Quinolones and use First line agents whenever possible:

Washoe County 2017 E. coli susceptibility:

98% Nitrofurantoin (Macrodantin) for 5 days
75% Trimethoprim/sulfa (Bactrim) for 3 days
approx. 90% * cefdinir BID for 5 days
Fosfomycin for one dose

(ciprofloxacin was only 78% susceptible)
Recent Study of antibiotic use in uncomplicated cystitis in 2 large private FP clinics with well insured patients

- 1546 visits—all women with any possible complicating factor were excluded—pregnancy, recurrent infection, antibiotic allergy, fever

- Prescribed Antibiotics:
  - 52% Fluoroquinolones—Cipro or levofloxacin (71% of these prescriptions were for 5 to 10 days of therapy, only 29% were for recommended 3 days)
  - 36% nitrofurantoin (70% were for one week of therapy)
  - 12% trimeth/sulfa (50% were for more than 5 days)

Conclusion—primary care physicians strongly prefer fluoroquinolones and prescribe longer courses of therapy than recommended in Guidelines
Symptom-Free Pee: LET IT BE

A national initiative to stop inappropriate antibiotic use for asymptomatic bacteriuria in long-term care residents.

Asymptomatic bacteriuria (bacteria in the urine with no symptoms) is colonization of the bladder that occurs frequently in the elderly, especially those with diabetes, immobility, incontinence, prostatic enlargement, or post-menopausal changes.

ANTIBIOTICS NOT INDICATED!
Asymptomatic bacteriuria is not an infection
○ Do not test urine even if foul-smelling, dark, or cloudy

For hemodynamically stable residents with cognitive changes, seek other causes: drug interactions / side effects, dehydration, sleep disturbances, sensory deprivation, hypoxia, hypoglycaemia, constipation, etc.

Note: Falls, decreased appetite, verbal aggression, wandering, confusion, and disorientation alone are not indications for urine testing.

HOLD URINE TESTING:
○ Monitor frequently
○ Rehydrate / push fluids for
○ 24 hours if not contraindicated

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
  - Gross hematuria

Dipsticks are not recommended due to poor predictive value. Urine culture ideally should be submitted in preservative.

IT IS HARD TO IGNORE A POSITIVE URINE TEST...

Unnecessary testing in colonized residents results in unnecessary antibiotics, which lead to adverse events (antibiotic resistance / failure, C. difficile infection, GI upset, etc.)

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

AMMI Canada
Symptom-Free Pee: LET IT BE

A national initiative to stop inappropriate antibiotic use for asymptomatic bacteriuria in long-term care residents.

STOP treating asymptomatic bacteriuria; it is not an infection
STOP testing foul-smelling, dark, or cloudy urine

WAIT and rehydrate residents who develop changes in mental status, behaviour, or function without typical urinary tract infection symptoms

GO to urinalysis and urine culture if typical signs and symptoms of urinary tract infection are present

For more directions and guidance:
www.ammi.ca
#SymptomFreeLetItBe
Hospital ASP programs are modifying this handout to fit their site.
There is growing medical and public awareness that the fluoroquinolones are potentially toxic drugs. New serious toxicities are still being identified.

Highest risk patients are elderly, on treatment for diabetes, have renal insufficiency, PPI use, hospitalized patients.

The greatest overuse of these drugs are in treatment of uncomplicated UTIs and asymptomatic bacteriuria, both in using them in the first place and then prescribing them for a longer course than indicated. Should also not be first line treatment for sinusitis or acute bronchitis.

Would be difficult to defend a fluoroquinolone Rx. in court if prescribed outside of guidelines and a serious complication develops.
II. No role for antibiotics in treatment of acute bronchitis in healthy patients
Bronchitis (uncomplicated)

<table>
<thead>
<tr>
<th>Key Symptoms</th>
<th>Key Clinical Findings</th>
<th>Antibiotic Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough, possible phlegm production</td>
<td>Differentiate from severe illness: pneumonia (abnormal vital signs, focal lung consolidation), pertussis (confirmed exposure or positive test), influenza (high fever, myalgias)</td>
<td>Antibiotics not recommended; Cough duration or change in sputum color is not indicative of bacterial infection</td>
</tr>
</tbody>
</table>
No benefit to antibiotics in uncomplicated acute bronchitis

Carl Llor et al. BMJ 2013;347:bmj.f5762

- **Objective** To evaluate the efficacy of oral anti-inflammatory or antibiotic treatment compared with placebo in the resolution of cough in patients with uncomplicated acute bronchitis and discolored sputum.

- **Design** Multicenter, parallel, single blinded placebo controlled, randomized clinical trial.

- **Setting** Nine primary care centers

- **Participants** Adults aged 18 to 70 with presenting symptoms associated with respiratory tract infection of less than one week’s duration, with cough as the predominant symptom, the presence of discolored sputum, and at least one other symptom of lower respiratory tract infection (dyspnea, wheezing, chest discomfort, or chest pain).

- **Interventions** Patients were randomized to receive either ibuprofen 600 mg three times daily, amoxicillin-clavulanic acid 500 mg/125 mg three times daily, or placebo three times daily for 10 days. The duration of symptoms was measured with a diary card.

- **Main outcome measure** Number of days with frequent cough after the randomization visit.
Fig 2 Kaplan-Meier survival analysis of days with frequent cough—that is, time (days) with cough from baseline visit until patient last scored ≥1 for both daytime and night time cough.

Carl Llor et al. BMJ 2013;347:bmj.f5762

The graph shows a Kaplan-Meier survival analysis with the percentage of patients with cough over time. The groups compared are Amoxicillin-clavulanic acid, Ibuprofen, and Placebo. The log rank test is 0.25, indicating no significant difference among the groups.

The table below shows the number of patients at risk for each group over the days:

<table>
<thead>
<tr>
<th>Days</th>
<th>Amoxicillin-clavulanic acid</th>
<th>Ibuprofen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>124</td>
<td>130</td>
<td>136</td>
</tr>
<tr>
<td>25</td>
<td>112</td>
<td>113</td>
<td>125</td>
</tr>
<tr>
<td>20</td>
<td>67</td>
<td>59</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

©2013 by British Medical Journal Publishing Group
## Provider Scripting for Cold/Flu/Upper Respiratory Infections and Antibiotics

<table>
<thead>
<tr>
<th>Don’t</th>
<th>Do Say</th>
</tr>
</thead>
</table>
| **Ask questions such as:** | • “Tell me about your symptoms.”
| • “Why are you here?” | • “What symptoms are you having?”
| • “What do you need?” | • “You have a virus.”
| • “How can I help you today?” | • “Antibiotics will not help you feel better because your illness is viral.”

| Minimize their illness: | • “You have an upper respiratory infection. This is caused by a virus. It can make you feel really bad for a few weeks, but there are some things we can do to help you feel better.”
| • “It’s just a virus/cold.” | • “Getting plenty of rest is important to help fight viruses. If you push yourself too hard, it may take longer for you to get better.”
| • “You have to let this run its course.” | |

| Be indecisive: | • “You have a virus.”
| • “It’s probably a virus.” | • “Antibiotics will not help you feel better because your illness is viral.”
| • “Antibiotics probably won’t help” | • “You have an upper respiratory infection which is caused by a virus.”
| • “Most upper respiratory infections are caused by viruses.” | |
Patient Materials

Antibiotics Aren’t Always the Answer.

What is the right way to take antibiotics?
If you need antibiotics, take them exactly as prescribed.
Improving the way healthcare professionals prescribe antibiotics, and the way we take antibiotics, helps keep our health system, helps fight antibiotic resistance, and assures that these life-saving drugs will be available for future generations.

Talk with your doctor if you have any questions about your antibiotics, or if you develop any side effects, especially diarrhea, which could be Clostridium difficile infection (also called C. difficile or C. diff), which needs to be treated. C. diff can lead to severe colon damage and death.

What are the side effects?
Common side effects range from minor to very serious health problems and can include:
- Rash
- Diarrhea
- Nausea
- Diarrhea
- Yeast infections

More serious side effects can include:
- Clostridium difficile infection
- Severe and/or life-threatening allergic reactions

To learn more about antibiotic prescribing and use, visit www.cdc.gov/antibiotic-use.

Symptom Relief for Viral Illnesses

1. DIAGNOSIS
   - Cold or cough
   - Middle ear fluid
   - Pneumonia
   - Pus
   - Viral lung disease
   - Bronchitis
   - Other

   You have been diagnosed with an illness caused by a viral ANTIBIOTICS do not work on viruses. Which medications should you and the side effects could still hurt you. The treatments prescribed here are not likely to be effective.

2. GENERAL INSTRUCTIONS
   - Drink extra water and fluids.
   - Use a cool mist vaporizer or saline nasal spray to relieve congestion.
   - For some threats in older children and adults, take ibuprofen, aspirin, or naproxen.
   - Use honey to relieve cough. Do not give honey to an infant younger than 1.

3. SPECIFIC MEDICATIONS
   - Fever or chills:
   - Ibuprofen
   - Paracetamol
   - Sinus and cold medications

   Use medicine according to the label, instructions, or as directed by your healthcare provider. Stop the medicine when the symptoms get better.

   signed: __________________

To learn more about antibiotic prescribing and use, visit www.cdc.gov/antibiotic-use.
III. Let’s give vancomycin a rest...

Is vanc/zosyn the answer for everything?
Major use in hospital is only for adding MRSA coverage or in patients with severe beta-lactam allergy.

Vancomycin: Spectrum

- **Gram-positive bacteria**
  - Methicillin-Susceptible AND Methicillin-Resistant *S. aureus* and coagulase-negative staphylococci
  - *Streptococcus pneumoniae* (including PRSP), viridans streptococcus, Group streptococcus
  - *Enterococcus* sp.
  - *Corynebacterium, Bacillus, Listeria, Actinomyces*
  - *Clostridium* sp. (including *C. difficile*), *Peptococcus*, *Peptostreptococcus*

- **No activity against gram-negative aerobes or anaerobes**
Some studies have suggested nephrotoxicity related to Vancomycin trough levels.

The graph shows the relationship between maximum Vancomycin trough levels and renal toxicity. The graph indicates a 25% reduction in GFR with different levels of maximum trough.

- 21% of cases with <15 mcg/ml
- 33% of cases with 15 to 20 mcg/ml
- 66% of cases with >20 mcg/ml

Statistical significance: $p<0.001$

“Nephrotoxicity during Vancomycin therapy in combination with Pip-Tazobactam or Cefepime” Rutter, W.C. et al.

- 4,193 patients - retrospective, matched cohort study over 4 year period (2010-4). Did not include patients on dialysis, preg, CKD, cystic fibrosis.
- When patients were matched on multiple factors-age, sex, contrast exposure, severity of illness, trough concentrations and multiple other confounding factors:
  - Adjusted AKI – Zosyn/vanco- 21.4%
  - Adjusted AKI- Cefep/vanco – 12.6% (P.<0001)
- “reinforces the need for judicious use of combination empirical anti-microbial therapy”
“Staphylococcus aureus
Community-acquired Pneumonia: Prevalence, Clinical Characteristics, and Outcomes” W.E. Self et al Clinical Inf Diseases May, 2016

- Vanderbilt University study that looked at prevalence of MRSA pneumonia in CAP patients (eliminated most HCAP type patients - recent hosp, dialysis, cancer, SNF etc) in 5 hospitals over 2.75 year period
- 2259 patients
- Approx. 30% of patients received initial anti-MRSA antibiotics – (vancomycin or linezolid)
- MRSA pna- only 0.9% had MRSA
- If admitted to ICU- 2.7% had MRSA
- If admitted to floor only 0.1% had MRSA!
- Bottom line- only 1 of 30 patients given empiric MRSA coverage for CAP actually had MRSA
- If a CAP patient is not sick enough for ICU, very unlikely to have MRSA pneumonia
MRSA Culture results Can drive Antibiotic De-escalation Society of CCM, Abstract 0692. presented Jan 23, 2017

- Mercy Hospital- St. Louis, Missouri. Retrospective chart review of randomly identified ICU patients in community hospital who were admitted and placed on empiric MRSA antibiotics as part of their initial regimen. All patients had sputum and blood cultures obtained before therapy started. Cultures were subsequently found to be negative in all patients. Did these antibiotics help even if cultures were negative?
- In 26 patients- stopped before 48 hours (average of 24 hours)
- In 28 patients- continued beyond 48 hours (average 5 days )
- No significant difference in APACHE III score or ICU mortality rate. No advantage to continued use of anti-MRSA antibiotics if cultures are negative- so consider stopping if no evidence of MRSA at 48 hours
From Dept of Pharmacy services, Henry Ford Hospital, Detroit MI

210 patients on anti- MRSA or antipseudomonal antibiotics for respiratory infection were studied. Studies have shown vancocin/piperacillin-tazobactam account for 20% of antibiotics prescribed for CAP.

Baseline 6 month period – non-pathogen containing sputum cultures were reported as “normal flora” only.

Next 6 month study period, negative sputum were now reported as “normal flora only, No S. aureus, MRSA or P. aeruginosa”. Also educated providers about this new reporting result.

After adjusting for severity etc., during the study period as compared to the baseline period, the new Lab comment was associated with a 5.7 fold increased odds of antibiotic de-escalation. Median 2 day decrease in broad spectrum coverage (stopping vancocin or zosyn) as compared to baseline period.

No mortality difference, significant decrease in acute kidney injury.

Spell out in your sputum culture result there is no MRSA present.
ER physician starts vancomycin and pip/tazobactam (Zosyn) for severe sepsis diagnosis
A few pointers to reduce vancomycin use

- A patient with CAP who isn’t in the ICU, isn’t spiking high fevers and doesn’t have cavities on CXR, is very unlikely to have MRSA pneumonia. Go with IDSA guidelines – ceftriaxone/azithromycin or doxycycline. Don’t use empiric vancomycin for these patients.

- If in ICU with pneumonia, and blood and sputum cultures do not show MRSA after 48 hours- stop the vancomycin. They don’t have MRSA pneumonia. Continuing does not improve outcome, just adds to risk of toxicity

- Don’t use vancomycin for non-purulent cellulitis- almost certainly strep. Try cefazolin, amp-sulbactam or simply ampicillin iv

- Remember ECHO talk on pseudo-cellulitis- 40% of “cellulitis” cases are not infectious- particularly if no fever and bilateral

- Try not to use empiric vanco/zosyn- too high risk for nephrotoxicity
We all know it seems sometimes, no matter what we do, the same people are making the same mistakes everyday, over and over for all eternity....

- But look on the bright side- at least we have job security
- Enjoy the Holidays!