Bugs and Drugs: Antibiotic Update
Kentucky Coalition of Nurse Practitioners and Nurse Midwives
April 27, 2019
Melinda C. Joyce, Pharm.D., FAPhA, FACHE

Disclosure
Melinda C. Joyce “declare(s) no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.”

Objectives
1. Discuss antimicrobial resistance and prudent prescribing
2. Describe the various classes of antibiotics, including potential adverse reactions, contraindications, or precautions
3. Review the microorganisms most likely implicated in common types of infections
4. Outline the most appropriate antibiotic treatment for common infections

Why the Emphasis on Prudent Use of Antibiotics?
- Improving antibiotic prescribing in all healthcare settings is critical to combating antibiotic-resistant bacteria
- Antibiotic resistance is considered to be among the greatest public health threats
- More than 2 million infections and over 23,000 deaths are attributed to infections caused by resistant organisms
- Drug choices for many bacterial infections are becoming more limited, expensive, and in some cases, non-existent
- New antibiotics to treat these resistant organisms are slow to be developed

What is a “Superbug”?
A “Superbug” is an organism that shows significant antibiotic resistance, usually to two or more classes of antibiotics.

A clear area around the disc represents “zone of inhibition” or sensitive to that antibiotic.

CDC Hot List for Resistant Organisms
- **Urgent Threats**
  - High consequence antibiotic-resistant threats
  - May not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission
  - *Clostridium difficile*
  - *Carbapenem-Resistant Enterobacteriaceae (CRE)*
  - *Neisseria gonorrhoeae*
    - Over 30% of cases are drug-resistant, including resistance to tetracycline, ceftriaxone, and azithromycin

[www.cdc.gov](http://www.cdc.gov)
CDC Hot List for Resistant Organisms

- **Serious Threats**
  - Not considered to be urgent, but may worsen and become urgent without ongoing monitoring and prevention activities
  - Multidrug-Resistant Acinetobacter
  - Drug-Resistant Campylobacter
  - Fluconazole-Resistant Candida
  - Extended Spectrum Enterobacteriaceae (ESBL)
  - Vancomycin-Resistant Enterococcus (VRE)
  - Multidrug-Resistant Pseudomonas aeruginosa
  - Drug-Resistant Non-Typhoidal Salmonella
  - Drug-Resistant Salmonella Serotype Typhi
  - Drug-Resistant Shigella
  - Methicillin-Resistant Staphylococcus aureus (MRSA)
  - Drug-Resistant Streptococcus pneumoniae
  - Drug-Resistant Tuberculosis

- **Concerning Threat**
  - Current threat of antibiotic resistance is low and/or there are multiple options for treatment
  - Ongoing monitoring is necessary to help prevent an outbreak
  - Vancomycin-resistant Staphylococcus aureus (VRSA)
  - Erythromycin-resistant Streptococcus Group A
  - Clindamycin-resistant Streptococcus Group B

Factors Contributing to Resistance

1. Use and overuse of antibiotics
2. More complex, higher acuity patients
3. Use of antibiotics in agriculture
4. Improper use of antibiotics
   - Treatment of viral infections
   - Sharing antibiotics
   - Not completing full regimens
   - Inadequate dosing
5. Passing infections from person to person, via contact or fomites

Outpatient Settings

- Nationally, antibiotic prescribing in outpatient settings decreased by 5% from 2011 to 2014
- Regional variation
- Approximately 269 million antibiotic prescriptions were dispensed from outpatient pharmacies in the United States
  - Enough for five out of every six people to receive one antibiotic prescription each year
  - At least 30% of these antibiotic prescriptions were unnecessary
  - At least 50% were unnecessary for acute respiratory conditions
- National goal is to reduce inappropriate outpatient antibiotic use by 50%

Community Antibiotic Prescriptions per 1,000 Population by State - 2015

Each year 269,5 million antibiotic prescriptions are written in the United States; enough to give 4 out of every 5 people one prescription.
Mechanisms of Antibiotic Resistance

- Bacteria may be resistant through two types
  - **Intrinsic Resistance** – the antibiotic never had activity against the bacterial species
    - Gram-negative organisms and vancomycin
  - **Acquired Resistance** – the antibiotic was originally active against the bacterial species but the genetic makeup of the bacteria has changed so that the antibiotic is no longer effective
- One or many mechanisms may exist in an organism
- Bacteria can copy and share resistance and may even combine the resistance with other types of resistance
- Multidrug-resistant bacteria often have multiple mechanisms

Mechanisms of Resistance

3. Changing the metabolic pathway
   - Some sulfonamide-resistant bacteria do not need para-aminobenzoic acid (PABA) for the synthesis of folic acid and nucleic acids
   - Likely to be responsible for the resistance seen with the macrolides and *Streptococcus pneumoniae* and *Neisseria gonorrhoea*

4. Decreased drug concentrations
   - Decreasing the permeability of the bacterial cell to the antibiotic or increasing the excretion of the drug from the cell surface
   - Efflux pumps

Drug Inactivation or Modification

- Predominant mechanism of resistance
- β-lactamases
  - Multiple types:
    - Simple, extended spectrum β-lactamases (ESBL), cephalosporinases, carbapenemases
    - Confer resistance to some, many, or all beta-lactam antibiotics
    - More potent in gram-negative bacteria
  - Examples:
    - *S. aureus*, *H. influenzae*, *N. gonorrhoeae*, *E. coli*, *Klebsiella* sp., *Enterobacter* sp., *Serratia* sp., other enteric bacteria, anaerobes

Extended Spectrum β-lactamases (ESBLs)

- β-lactamases capable of hydrolyzing extended spectrum cephalosporins, penicillins, and aztreonam
- Most often associated with *E. coli* and *Klebsiella pneumoniae* but spreading to other bacteria
- Usually plasmid mediated
- Aminoglycoside, ciprofloxacin and trimethoprim-sulfamethoxazole resistance often encoded on same plasmid
- Has become a significant resistance determinate in acute and long-term care facility enteric pathogens

Multidrug Resistant Gram-Negative Organisms

- Defined as resistant to one or more classes of antimicrobial classes
- Severely limits treatment options and the incidence of resistance is rising
- Widespread use of cephalosporins and beta-lactam combination antibiotics has led to extended-spectrum beta-lactamases (ESBLs), which are resistant to both of those classes
- Carbapenems have been the only effective agents for ESBLs
- Emergence of carbapenemases, such as *Klebsiella pneumoniae* carbapenemase (KPCs) are threatening carbapenems as the antibiotics of last resort
- Often responsible for causing healthcare-acquired urinary tract infections and pneumonia
- Reason that the CDC is concerned about the use of carbapenems in the hospital setting

www.cdc.gov
Multidrug Resistant Gram-Negative Organisms

- Some Acinetobacter strains are resistant to nearly all or all antibiotics including the carbapenems
  - About 63% are resistant to at least three different antibiotic classes
  - Overall, approximately 2% of healthcare-associated infections are caused by Acinetobacter
  - Proportion of Acinetobacter infections in critically ill patients on mechanical ventilators is about 7%
  - Responsible for about 500 deaths each year

Carbapenem-Resistant Enterobacteriaceae (CRE)

- Most common in Klebsiella pneumoniae (KPC)
- Also seen in E. coli, Enterobacter, Citrobacter, Salmonella, Serratia, Pseudomonas, and Proteus spp.
- CRE are bacteria that are resistant to most antibiotics
- These bacteria can cause pneumonia, urinary tract infections, and bloodstream infections
- Most often seen in hospitalized, critically ill patients
  - Almost half of the hospitalized patients with CRE bloodstream infections die
  - There are very few antibiotics that are available to treat infections caused by CRE
  - Meropenem (Merrem); tigecycline (Tygacil) as adjunct therapy; colistin

Improve Prescribing of Antibiotics

- Incorrect Diagnosis
  - Antibiotics given when the infection is viral and are not needed
  - Antibiotics given without symptoms, such as asymptomatic bacteriuria
  - Treating colonization or contamination – not an actual infection
- Incorrect Prescription
  - The wrong antibiotic is given to treat an infection
  - Given at the wrong dose (sub-therapeutic dosing)
  - Broad spectrum agents used to treat bacteria that are susceptible to many other narrow-spectrum agents
- No De-Escalation
  - Continuing antibiotics when they are no longer necessary
  - Continuing IV antibiotics when the patient can tolerate an equivalent oral antibiotic

Improve Use of Antibiotics

- Patient Issues
  - Not completing the full course of the antibiotic
  - Keeping antibiotics at home “just in case someone in the family needs them”
  - “Doctor shopping” to find a provider that will prescribe antibiotics
  - Not staying home or away from others when ill
- Agricultural Issues
  - Use of antibiotics in livestock to prevent disease
  - Low-dose antibiotics have also been associated with a method for animal weight gain
  - It is thought that resistant strains of salmonella, campylobacter, enterococcus, and E. coli have been transmitted from animals to humans

Common Infections

Upper Respiratory Infections
Upper Respiratory Tract Infections (URIs)

- One of the most frequent infectious disease reasons for outpatient visits
- Symptoms are those of the common cold
  - Cough, sneezing, congestion, lethargy
- A variety of illnesses comprise URIs
  - Otitis media – inflammation of the middle ear
  - Rhinosinusitis – inflammation and/or infection of the paranasal sinuses
  - Pharyngitis – acute infection of the oropharynx or nasopharynx
- Most are viral in nature
  - Rhinovirus
  - Enterovirus
- Antibiotics should be avoided unless there are compelling reasons for their use

Acute Otitis Media

- Most common childhood infection for which antibiotics are prescribed
- Acute otitis media has a sudden onset of signs and symptoms
- Definitive diagnosis requires either
  - Moderate or severe bulging of tympanic membrane or new onset ototrahea not due to otitis externa
  - Mild bulging of the tympanic membrane AND recent (<48 hours) onset of otalgia or intense erythema of the tympanic membrane
- Watchful waiting in most cases is sufficient as most cases are viral
- Most children become asymptomatic by day 7

Acute Otitis Media

- Ibuprofen or acetaminophen are the best options for pain control
- Use care in recommending over-the-counter cough/cold preparations considering that many products are combinations
  - Most contain acetaminophen – watch the total dose of acetaminophen
- Decongestants and antihistamines should not be used for acute otitis media due to lack of benefit and increased risk of side effects
  - Watchful waiting is encouraged!!

Antibiotics for Acute Otitis Media

- Amoxicillin 80 to 90 mg/kg/day for 10 days remains first-line therapy for children who have not received amoxicillin within the last 30 days
- If no response in 72 hours, consider alternative agents
  - Amoxicillin/clavulanate is recommended if the child has had amoxicillin within the last 30 days or if there is concurrent purulent conjunctivitis
  - For penicillin allergic, second or third generation cephalosporins may be appropriate
- Resistance is more likely to be seen:
  - Attendance at day care
  - Antibiotic use within the last 30 days
  - Age younger than 2 years

Rhinosinusitis

- Most cases are viral
  - In both adults and pediatrics, 90 to 98% of cases are viral
  - Resolves in about 7 days
- Diagnose acute bacterial rhinosinusitis based on symptoms that are:
  - Severe (>3-4 days), such as fever > 39 C and purulent nasal discharge or facial pain
  - Persistent (>10 days) without improvement, such as nasal discharge and daytime cough or
  - Worsening (3-4 days) such as worsening or new onset fever, daytime cough, or nasal discharge after initial improvement (double-sickening)
- Sinus radiographs are not routinely recommended
  - Watchful waiting is encouraged!!

Non-Pharmacological/ Supportive Care

Non-Bacterial Rhinosinusitis

- Topical Nasal Decongestants
  - Reduce inflammation through vasoconstriction
- Oral Decongestants
  - Reduce inflammation through vasoconstriction
- Irrigation of Nasal Sinus
  - Increase mucosal moisture

Bacterial Rhinosinusitis

- Avoid decongestants and antihistamines
  - Symptoms usually do not respond
- Irrigation of Nasal Sinus
  - Increase mucosal moisture
- Inhaled corticosteroids can be used in patients with a history of allergic rhinitis
Antibiotics for Sinusitis

- Treatment should be continued for 10 to 14 days
- For milder infections
  - Penicillins, such as amoxicillin/clavulanate are recommended as first-line therapy
  - If penicillin allergic, doxycycline or a second or third generation cephalosporin may be used
- For more serious infections
  - Macrolides, such as azithromycin are not recommended due to high levels of Streptococcus pneumoniae resistance (>40%)
- If the patient cannot tolerate oral medication, a single dose of ceftriaxone may be used
- For more serious infections
  - Amoxicillin/clavulanate (high dose)
  - Quinolone with antipneumococcal activity, such as levofloxacin

Acute Pharyngitis

- One of the four most common episodic clinic visits
- May be viral or bacterial
  - Group A beta-hemolytic streptococcal (GABHS) infection is the only common indication for antibiotic therapy for sore throat
- Streptococcal
  - Only 5-10% of adult cases of acute pharyngitis are caused by GABHS
  - Streptococcal pharyngitis is most commonly seen in children aged 5 to 15 years and is rare in pre-school children
  - Most likely to be seen in late winter/early spring
  - Sudden onset with severe sore throat
- Viral
  - Can be seen at any time of the year
  - Mild sore throat, often accompanied by cough, rhinitis, hoarseness, and myalgias

Pharyngitis

- Lab tests will determine if the pharyngitis is bacterial
  - Rapid Streptococcal Antigen Detection Test (RADT)
    - May be more prone to false negatives
  - Need two or more criteria for testing
    - History of fever
    - Lack of cough
    - Tonsillectomy
    - Tender anterior cervical adenopathy
  - Patients with none or only one of these symptoms should not be tested or treated for GABHS
  - Testing is generally not done on adults or children under the age of 3
  - In children or adolescents with a negative RADT, should be backed up with a throat culture

Pharyngitis

- Treatment
  - No antibiotics when viral (when RADT results are negative)
  - Recommended treatment with antibiotics is 10 days if bacterial
  - Penicillin VK or Amoxicillin is recommended for initial treatment of GABHS
  - If the patient is penicillin allergic:
    - First generation oral cephalosporin, such as cephalaxin or cefadroxil
    - Clindamycin
  - Fluoroquinolones are NOT appropriate

Acute Bronchitis

- Infection of the tracheobronchial tree that causes reversible bronchial inflammation
- Most patients will present with cough and symptoms can last from 7 days to longer than 14 days
- Bronchitis is often thought of as a diagnosis of exclusion (rule out more serious causes of cough)
- Colored sputum does NOT automatically indicate a bacterial infection
- Acute bronchitis is different than chronic bronchitis, which is a component of chronic obstructive pulmonary disease
Treatment Options for Bronchitis

- No antibiotics!
  - May be considered IF patient has persistent fever and respiratory symptoms for greater than 6 days
  - Immunocompromised
  - Antibiotic should be directed toward anticipated pathogen
  - Increase hydration
  - Mist therapy
  - Antipyretics to help improve malaise and fever symptoms
  - Beta-agonists, such as albuterol IF patient has moderate wheezing
  - Antitussive therapy is not routinely recommended, but may be helpful in patients with severe sleep disturbances because of coughing

Pneumonia

- Common lower respiratory tract infection that causes inflammation of the lung parenchyma
- Most common cause of death from an infectious disease in the United States
- The lung is not sterile – bacteria are diverse
- The defense mechanisms of the lung usually help to prevent passage of foreign materials
  - Disease states, such as COPD
  - Age
  - Smoking
- Immunization!
  - Pneumococcal vaccination will help to decrease incidence and severity of susceptible strains of pneumonia
  - Annual influenza vaccination is very important as pneumonia can be a secondary infection behind the flu

Community-Acquired Pneumonia (CAP)

- Symptoms
  - Fever
  - Shortness of breath
  - Cough
  - Tachypnea
  - Leukocytosis or leukopenia
- Most common pathogens
  - Streptococcus pneumoniae
  - Chlamydia pneumoniae
  - Mycoplasma pneumoniae
  - Legionella spp
  - Haemophilus influenzae

Empiric Treatment for CAP

<table>
<thead>
<tr>
<th>Location</th>
<th>Non-ICU</th>
<th>ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously healthy and no antimicrobial therapy in the previous 3 months</td>
<td>Macrolide OR Doxycycline</td>
<td>Respiratory Fluoroquinolone OR Beta-lactam plus Macrolide</td>
</tr>
<tr>
<td>Co-Morbidities (chronic illnesses, such as COPD, heart disease, or diabetes) or antimicrobial therapy in the previous 3 months</td>
<td>Respiratory Fluoroquinolone OR Beta-lactam plus Macrolide</td>
<td>Beta-Lactam plus Azithromycin OR Respiratory Fluoroquinolone plus Beta-lactam</td>
</tr>
<tr>
<td>Macrolide OR Doxycycline</td>
<td>Respiratory Fluoroquinolone OR Beta-lactam plus Macrolide</td>
<td>Respiratory Fluoroquinolone</td>
</tr>
<tr>
<td>Penicillin Allergy</td>
<td>Respiratory Fluoroquinolone</td>
<td></td>
</tr>
<tr>
<td>Respiratory Fluoroquinolone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment for CAP

- Treatment duration for CAP is a minimum of 5 days
- If the patient remains febrile for 2 to 3 days or fails to meet more than one sign of clinical stability, a longer treatment duration may be indicated
- Criteria for clinical stability
  - Temperature < 37.8°C
  - Heart rate < 100 beats/min
  - Systolic blood pressure >90 mmHg
  - Arterial oxygen saturation > 90% or pO2 > 60 mmHg on room air
  - Ability to tolerate oral mediation
  - Baseline mental status for patient

Hospital-Acquired Pneumonia/ Ventilator-Associated Pneumonia (HAP/VAP)

- HAP – defined as pneumonia that presents at least 48 hours following hospitalization
- Risk factors for multi-drug resistant organisms for HAP
- Previous IV antibiotic use within 90 days
- VAP – defined as pneumonia that presents at least 48 hours after intubation
- Risk factors for multi-drug resistant organisms for VAP
- Previous IV antibiotic use within 90 days
- Septic shock
- Acute respiratory distress syndrome prior to VAP onset
- 5 days of hospitalization prior to VAP onset
Empiric Treatment for HAP/VAP

<table>
<thead>
<tr>
<th>Antibiotics with MRSA Coverage</th>
<th>Beta-Lactam-based Antibiotics with Pseudomonas Coverage</th>
<th>Non-Beta-Lactam Antibiotics with Pseudomonas Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin 15 mg/kg IV q8-12h OR Linezolid 600 mg IV q12h</td>
<td>Piperacillin/Tazobactam 4.5 g IV q6h OR Ceftazidime 2 g IV q6h OR Meropenem 1 g IV q6h OR Aztreonam 2 g IV q6h</td>
<td>Levofoxacin 750 mg IV q24h OR Amikacin 15-20 mg/kg IV q24h OR Gentamicin 5-7 mg/kg IV q24h OR Tobramycin 5-7 mg/kg IV loading dose followed by 2.5 mg IV q12h</td>
</tr>
</tbody>
</table>

Skin and Soft Tissue Infections

Cellulitis

- Incision and drainage if an abscess
- Elevation and immobilization of the affected area
- Cool sterile saline dressings followed by moist heat
- Severe cases may require surgical intervention
- Antimicrobial therapy should be directed towards the type of bacteria, either documented or suspected
- Consider patient presentation for possible CA-MRSA
- Cultures can be helpful but must be obtained appropriately
- Underlying nutritional status is vital
- Also important to keep glucose levels under control
  - When glucose levels are consistently greater than 250 mg/dL, white blood cells do not work very well to fight infection

Antibiotics for Cellulitis

- Previously Healthy
  - Empirical treatment for staphylococcal or streptococcal cellulitis
  - Mild infections when MRSA is not suspected
    - Beta-lactam agent, such as dicloxacillin or a first-generation cephalosporin
  - Mild infections when MRSA is suspected or patient has a beta-lactam allergy
    - Clindamycin or
    - Doxycycline or
    - Minocycline or
    - Sulfamethoxazole/Trimethoprim

- Not Healthy due to:
  - Risk factors for multidrug resistant bacteria
  - Immunosuppression
  - Peripherial vascular disease
  - Pressure ulcers
  - Suspected polymicrobial infection
  - Therapy should provide wide coverage including MSSA, MRSA, GABHS, Enterobacter species, Pseudomonas, and anaerobes
  - Mild infections
    - Amoxicillin/clavulanate or
    - Levofloxacin plus clindamycin
  - Moderate to severe infections
    - MRSA coverage with Vancomycin, Daptomycin, or Linezolid PLUS
    - Gram-negative and anaerobic coverage, such as Piperacillin/Tazobactam plus Metronidazole plus Clindamycin

Clostridium difficile Infections
**Clostridium difficile Infections (CDI)**

- *C. difficile* is a spore-forming, gram-positive anaerobic bacillus that produces two exotoxins: toxin A and toxin B
- The organism produces the toxins that cause intense inflammation of the colonic mucosa
- It is a common cause of antibiotic-associated diarrhea (15-25%)
- 14,000 deaths attributed to CDI per year
- 90% of the deaths are in patients > 65 years of age
- Disruption of the bowel microflora, generally by antibiotics, creates an environment that allows *C. diff* to proliferate

**Risk Factors**

- Antibiotic exposure – type and duration – most important risk factor
  - Within the past three months
  - All antibiotic classes have been implicated
- History of a previous *C. diff* infection
- GI surgery/ manipulation
- NG tubes
- Enemas
- Use of proton pump inhibitors
- Long length of stay in institutions
- Serious underlying illnesses
- Immunocompromised
- Advanced age

**Treatment of *C. diff* Infections**

- Initial mild to moderate episodes (WBC <15,000)
  - Vancomycin 125 mg four times a day for 10 days OR
  - Fidaxomicin (Dificid) 200 mg twice daily for 10 days
- Initial severe episodes (WBC ≥ 150,000) or in situations where the offending antibiotics have to be continued
  - Oral vancomycin 125 mg four times a day for 10 days OR
  - Fidaxomicin 200 mg twice daily for 10 days
- Initial severe disease with hypotension or shock, ileus or megacolon
  - Vancomycin 500 mg four times a day by NG tube plus metronidazole 500 mg IV q8h
  - May require 6 weeks of pulsed dosing of oral vancomycin after the initial treatment is completed

**First recurrence**

- Vancomycin 125 mg four times a day if metronidazole was used as the initial antibiotic treatment
- Fidaxomicin 200 mg twice daily if vancomycin was used as the initial antibiotic treatment
- Likely to require pulsed vancomycin dosing for 6 weeks
  - Vancomycin 125 mg four times per day for 10-14 days, then two times per day for 7 days, then once per day for 7 days, then every 2 to 3 days for 2-8 weeks

**Second recurrence**

- Fidaxomicin 200 mg twice daily for 10 days if vancomycin was previously used
- Vancomycin pulsed dosing for 6 weeks
- Vancomycin extended treatment
  - 125 mg once daily for 6 months
- Bezlotoxumab (Zinplava) has been shown to significantly reduce the risk for recurrence in certain patient populations
- Fecal microbiota transplantation

**Oral agents preferred but may use IV metronidazole only if patient cannot tolerate oral therapy**

- Probiotics have been studied for the prevention of *C diff* infections, but not currently recommended due to limited studies showing efficacy
- Likely to take 2 to 4 days of antibiotic therapy before the diarrhea stops
- No anti-motility agents
- Infection is considered resolved once the antibiotic regimen has been completed and the patient is diarrhea-free for 48 hours AFTER treatment has been completed
- Not necessary to do a "test of cure"
- Not necessary to test repeated samples during same episode of diarrhea
Fecal Microbiota Transplantation (Stool Transplant)

- Gaining more acceptance
- No standard administration approach
- Administration options include:
  - Enema/colonoscopy or through NG tube
  - NG tube approach has been studied the most
  - Stool slurry that needs to be used immediately from donor
  - Can be local donor or banked stool
  - 250 ml per NG x 2, about 12-24 hours apart
  - Fecal microbiota transplantation (FMT) capsules
  - 20 capsules ingested within 90 minutes

Fecal Microbiota Transplantation (FMT)

- Success is measured through resolution of symptoms and absence of relapse within 8 weeks
- Cost: $1500/ treatment
  - Is not covered by most insurance plans
  - Results from Med Center Health
    - Study of 52 patients
      - 95.7% (45/47) responded to FMT – NG tube approach
        - Two relapsed and both were placed on extended vancomycin for 6 months
      - 40% (2/5) responded to FMT – capsules
        - Three relapsed and 2 had FMT- NG and responded and one was placed on extended vancomycin

Bezlotoxumab (Zinplava)

- Monoclonal antibody which binds to Clostridium difficile toxin B and neutralizes it to prevent toxic effects
- Used to reduce recurrence of Clostridium difficile infections (CDI) in patients > 18 years of age who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence
- Not for treatment of CDI but to prevent recurrence
- It is not an antibiotic and must be used in conjunction with standard of care antibacterial treatment (metronidazole, vancomycin, or fidaxomicin)
- Patients should be cautioned to complete their full course of antibacterial treatment
- Should be used cautiously (if at all) in patients with heart failure
  - Can exacerbate heart failure symptoms
  - Expensive: $3800/ single dose

Bezlotoxumab

- Adverse Effects:
  - Exacerbation of heart failure (13%)
  - Headache (4%)
  - Nausea (7%)
  - Infusion-related reactions (10%) – including nausea, fatigue, fever, dizziness, headache, dyspnea, hypertension
- 10 mg/kg IV as a single dose during antibacterial treatment of the Clostridium difficile infection
  - No dosage adjustments for renal or hepatic impairment at this time
  - Should be infused over 60 minutes

Urinary Tract Infections

Pathogens

- E. coli causes 80% of all community-acquired UTIs and about half of UTIs in the hospital
- Other pathogens include gram-negative rods, such as Proteus, Klebsiella, and Enterobacter
- E. coli has become increasingly resistant to Trimethoprim/Sulfamethoxazole (TMX/ SMP) to where it is no longer a first line agent for complicated UTI or pyelonephritis
- Although the quinolones are used for complicated UTIs, more resistance is being seen with Enterococci
- Beta-lactams are associated with about a 40% resistance rate for E. coli
- Nitrofurantoin has low resistance, but has little use beyond the urinary tract because of poor tissue perfusion
Uncomplicated Cystitis

- Local symptoms only (frequency, urgency, painful urination)
- No fever or flank pain
- TMP/SMX twice daily for 3 days
- Nitrofurantoin twice daily for 5 days
- Avoid if resistance in area is greater than 20% or antibiotics taken in the previous 3 months
- Older patients or pregnant patients require 7 days of therapy
- If there are issues of resistance, prior antibiotic therapy or history of allergic reactions, then
  - Beta-lactams for 7 days
  - Fosfomycin as a single dose
  - Useful if compliance is likely to be an issue
  - Fluoroquinolones for 3 days
  - Last option

UTIs During Pregnancy

- In 20 to 40% of cases, UTIs during pregnancy are a progression of asymptomatic bacteriuria
- More likely to be a complicated UTI and may progress to pyelonephritis
- Safest antibiotics to use during pregnancy are: amoxicillin; amoxicillin-clavulanate; nitrofurantoin; and cephalaxin
- Resistance to the penicillins may be as high as 33%, so should not be used as first-line
- Nitrofurantoin should not be used in last trimester
- Duration of treatment may be 3 days if caught early but 7 to 10 days may be more appropriate

Complicated UTI

- Pre-disposing factors
  - Urinary obstruction
  - Incomplete bladder emptying due to anatomic or neurogenic causes
  - Foreign bodies
  - Systemic conditions
  - Male
- Treatment options
  - Fluoroquinolones for 7 to 14 days
  - Longer duration will depend on more severe symptoms or systemic infections
  - IV cephalosporins, such as ceftriaxone
  - Aminoglycosides
- Streamline once culture results are available
- Convert to oral therapy once patient can tolerate oral therapy

UTIs in the Elderly

- Symptoms may be atypical
  - Mental status changes in conjunction with other signs and symptoms
  - Lethargy
  - Weakness
  - Should have a compelling reason to get a urine culture
  - Foul smelling or cloudy urine with no other symptoms is not a reason
  - Important to assess renal function before prescribing antibiotics
- Patients that are otherwise healthy at home
  - Treat as uncomplicated cystitis
  - Duration of 7 days
- Long-term care patients with no catheter
  - Treat as uncomplicated cystitis
  - Duration of 7 days
- Long-term care patients with catheter
  - Treat as catheter-associated UTI

Asymptomatic Bacteriuria

- ≥10⁵ colony forming units is often used as a diagnostic criteria for a positive urine culture
- It does NOT prove infection; it is just a number to state that the culture is unlikely due to contamination
- Pyuria also is not predictive on its own
- It is the presence of symptoms AND pyuria AND bacteriuria that denotes infection
- No adverse outcomes associated with asymptomatic bacteriuria in older adults and there are no benefits associated with antibiotic treatment
- Asymptomatic bacteriuria should not be treated with antibiotics unless the patient is pregnant, undergoing urological surgery, or has received a kidney or kidney/pancreas transplant

Catheter-Associated UTIs (CAUTIs)

- Definition of CAUTI
  - Indwelling urethral or suprapubic catheter or intermittent catheterization
  - Presence of signs or symptoms of UTI with no other identified source of infection
  - ≥10⁵ CFU/ml of one bacterial species
  - Catheter urine specimen or midstream voided specimen if catheter was removed within 48 hours
- Treatment options
  - Ampicillin plus gentamicin
  - Piperacillin/Tazobactam
  - Fluoroquinolone
  - Carbapenem, if suspect an extended-spectrum beta-lactamase producing organism
- Treat for 7 days for most patients, but if a delayed response, 10 to 14 days may be required
Pyelonephritis

- A more severe infection, involving the upper urinary tract, including the kidneys
- Systemic symptoms that require prompt treatment to avoid progressing to urosepsis
- Treatment options
  - Patients not requiring hospitalization
    - Ceftriaxone (single dose) followed by either
    - Fluoroquinolone for 5 days or
    - TMP/SMX for 14 days
    - Beta-lactams should be avoided
  - Patients requiring hospitalization
    - Fluoroquinolone for 5 days or
    - Aminoglycoside plus Beta-Lactam or
    - Extended-spectrum Beta-lactam plus Aminoglycoside or
    - Carbapenem (if resistant organism suspected)
  - Other than fluoroquinolone, duration of therapy should be 10 to 14 days
  - Streamline once culture and sensitivity results available
  - Switch to oral therapy when indicated

Antibiotic Pearls

Established Risks of Antibiotic Use

- Increased infection risk
  - Clostridium difficile infection
  - Candida
  - Have started to see more resistant strains of Candida, especially in hospitalized patients
- Allergic reactions
- Drug interactions
- Antibiotic resistance

Beta-Lactam Antibiotics

- Penicillins
  - Some forms may have limited use because of resistance
  - Addition of a beta-lactam inhibitor, such as clavulanic acid or tazobactam are beneficial in treating resistant organisms
  - Resistance can develop by a variety of mechanisms
  - Dose may need to be adjusted for impaired renal function
  - Newer information emerging regarding increased nephrotoxicity when vancomycin is given in combination with piperacillin/tazobactam
  - Hypersensitivity reactions and rash are common

Penicillin Skin Testing

- Allergy to penicillin and related antibiotics is the most commonly reported drug allergy in the United States
- Several studies have shown that many people that report a penicillin allergy are not truly allergic when tested
- There are several protocols available and can usually be done in about 45 minutes
- Benzylpenicilloyl polylysine injection (Pre-Peri) is currently the only FDA-approved skin test for the diagnosis of penicillin allergy
- Can open up more options for antibiotics, especially to help decrease the use of vancomycin
### Beta-Lactam Antibiotics

- **Carbapenems**
  - Not all agents are the same
  - Ertapenem – notable omissions in the spectrum of activity of this agent; No coverage against *Pseudomonas aeruginosa*; *Acinetobacter; methicillin-resistant staphylococci; Enterococcus species
  - Should not be used for surgical prophylaxis
  - Doripenem – concern about use in pneumonia as studies have shown a 23% higher mortality
  - All carbapenems should be used very carefully due to the development of carbapenamases
  - Resistance can develop from several mechanisms
  - Should be used very sparingly for specific indications

### Protein Synthesis Inhibitors

- **Aminoglycosides**
  - Narrow spectrum of activity
  - More resistance noted, especially with gentamicin and tobramycin
  - Necessary to monitor and adjust dosage for renal impairment
  - Serum drug concentrations are beneficial
  - Numerous adverse effects
    - Ototoxicity
    - Nephrotoxicity
    - Neurotoxicity
    - Pregnancy

### Plazomicin (Zemdri)

- **Parenteral aminoglycoside indicated for the treatment of complicated urinary tract infections, including pyelonephritis in patients over the age of 18 years**
  - Should be reserved for situations of resistant organisms
  - Susceptible organisms include:
    - *E. coli; Klebsiella pneumoniae; Proteus mirabilis; Enterobacter cloacae*
  - Available in 10 ml vials of 500mg/10 ml (50 mg/ml)
  - Same contraindications as other aminoglycosides
  - Adverse Effects
    - Nephrotoxicity (boxed warning)
    - Ototoxicity (boxed warning)
    - Neuromuscular blockade (boxed warning)
    - Diarrhea
    - Blood pressure changes

### Eravacycline (Xerava)

- **Parenteral tetracycline indicated for the treatment of complicated intra-abdominal infections in patients aged 18 years and older**
  - Should not be used in pediatric patients
  - Not recommended during 2nd or 3rd trimester of pregnancy
  - Not recommended during and for 4 days after last dose for nursing mothers
  - Is not indicated for the treatment of complicated urinary tract infections
  - Susceptible organisms include:
    - *E. coli; Klebsiella pneumoniae; Citrobacter freundii; Enterobacter; Enterococcus*
  - Available in vials of 50 mg for reconstitution

### Plazomicin

- **Dose:**
  - Dependent on renal function
  - Drug should be infused over 30 minutes
  - CrCl ≥ 60 ml/min: 15 mg/kg every 24 hours for 4 to 7 days
  - CrCl 30 to < 60 ml/min: 10 mg/kg every 24 hours
  - CrCl 15 to < 30 ml/min: 10 mg/kg every 48 hours
  - CrCl ≤ 15 ml/min: Not recommended for use
  - Monitor trough level within 30 minutes prior to second dose
  - Trough level should be < 3 mcg/ml
  - If ≥ 3 mcg/ml, extend dosing interval
    - From 24 hours to 36 hours
    - From 48 hours to 72 hours
  - Monitor for other ototoxic or nephrotoxic medications

### Protein Synthesis Inhibitors

- **Tetracyclines**
  - Broad spectrum antibiotics that have activity against gram-positive, gram-negative, and atypical microorganisms
  - Numerous adverse effects
    - GI, most common
    - Photosensitivity
    - Impact on teeth, especially in children
    - Potential drug-drug and drug-food interactions
    - Contraindicated in pregnant women and children
  - Teeth and bone impact from binding with calcium
  - Unused tetracyclines should be discarded to prevent Fanconi-like renal toxicity on proximal renal tubules resulting from ingestion of outdated and degraded tetracycline

### Eravacycline

- **Dose:**
  - Dependent on renal function
  - Drug should be infused over 30 minutes
  - CrCl ≥ 60 ml/min: 15 mg/kg every 24 hours for 4 to 7 days
  - CrCl 30 to < 60 ml/min: 10 mg/kg every 24 hours
  - CrCl 15 to < 30 ml/min: 10 mg/kg every 48 hours
  - CrCl ≤ 15 ml/min: Not recommended for use
  - Monitor trough level within 30 minutes prior to second dose
  - Trough level should be < 3 mcg/ml
  - If ≥ 3 mcg/ml, extend dosing interval
    - From 24 hours to 36 hours
    - From 48 hours to 72 hours
  - Monitor for other ototoxic or nephrotoxic medications
Eravacycline

- **Dose:**
  - 1 mg/kg, infused over approximately 60 minutes every 12 hours for 4-14 days
  - Does need to be dose-adjusted to every 24 hours after two initial doses for patients with severe hepatic dysfunction

- **Drug Interactions**
  - May be antagonized by strong CYP 3A4 inducers (such as rifampin or phenobarbital)
  - May need to increase dose to 1.5 mg/kg every 12 hours
  - May enhance the effects of warfarin, necessitating a decrease in the warfarin dose

Eravacycline

- **Adverse Effects**
  - Infusion site reaction (8%)
  - Nausea (7%)
  - Vomiting (4%)
  - Diarrhea (2%)
  - Hypotension (1%)
  - Tooth discoloration
  - Increase in BUN
  - Abnormal liver function tests

Omadacycline

- **Tetracycline indicated for:**
  - Community-acquired bacterial pneumonia
  - Acute bacterial skin and skin structure infections (ABSSSI)
  - Should not be used in pediatric patients
  - Not recommended during 2nd or 3rd trimester of pregnancy
  - Not recommended during and for 4 days after last dose for nursing mothers
  - Susceptible organisms include:
    - Staphylococcus aureus (including MRSA); Klebsiella pneumoniae; ; Enterobacter; Enterococcus; Legionella pneumophilia; Haemophilus influenzae; Mycoplasma pneumonia; Chlamydophila pneumoniae
    - Available in vials of 100 mg for reconstitution and 150 mg tablets

Omadacycline

- **Drug Interactions:**
  - Similar to other tetracyclines
  - May enhance the effects of warfarin, necessitating a decrease in the warfarin dose
  - Antacids, calcium or iron-containing preparations should be separated from the administration of the omadacycline by several hours
  - Adverse Effects:
    - Nausea – may be as high 22% with vomiting as high as 11%
    - Local injection site reactions (5%)
    - Hypertension (3%)
    - Insomnia (3%)
    - Headache (2%)

Omadacycline

- **Dose:**
  - For CAP or for ABSSSI:
    - 200 mg IV infused over 60 minutes on day 1, followed by 100 mg IV daily for 7 to 14 days
    - Can de-escalate to 300 mg orally once daily for the remainder of treatment once the patient can tolerate oral
    - For oral only: 450 mg orally on days 1, followed by 300 mg orally once daily for 7 to 14 days

DNA Inhibitor

- **Fluoroquinolones**
  - Clinically active against most gram-positive and gram-negative organisms (very broad spectrum)
  - Many indications for use
  - Same effect either PO or IV
  - Dose should be adjusted for renal impairment
  - Starting to see more issues with resistance
    - May be more problematic with ciprofloxacin
    - Not indicated for children under the age of 16, unless compelling reason for use
  - Can be responsible for resistance patterns with other organisms due to overuse
  - Watch for potential drug-drug interactions
Fluoroquinolone Side Effects

- Boxed warnings about the potential for significant adverse effects
- Hyperglycemia/Hypoglycemia – considered to be one of the most clinically important adverse effects
  - Risk varies between agents and between patients
  - Monitor blood glucose levels in patients who are also taking an oral hypoglycemic agent or insulin
- CNS effects
  - Memory impairment
  - Dizziness
  - Headache
  - Confusion
  - Hallucinations (more common at higher doses)

- Double vision
- Peripheral neuropathy – rare, but could be permanent
- Tendon issues – inflammation and possible rupture
  - Achilles tendon most likely impacted
- QT-interval prolongation
- Phototoxicity
- May exacerbate muscle weakness associated with myasthenia gravis
- Should be avoided in pregnancy

Parting Thoughts

General Approach for Prudent Prescribing

- Confirm Infection
- Perform Diagnostic Tests/ Workup
- Start Empiric Therapy
  - If warranted
  - Remember “watchful waiting”
- Re-Evaluate/ Monitor Response to Therapy
- Streamline/ Narrow Antimicrobial Therapy
  - If the gut works, use it!
  - It is okay to say “No”

Prudent Prescribing

- Choice of antibiotic should be based on organism
- Do not give antibiotics with overlapping activity
- Prevent infection
  - Use good hand hygiene and infection control practices
  - Consider whether or not a central line or a Foley catheter is really needed
  - Make sure all antibiotic prescriptions have a stop date
  - Including orders in the hospital or long-term care setting

Conclusions

- Antibiotics clearly save lives but resistance is costing lives
- Poor prescribing of antibiotics are putting patients at unnecessary risk
  - Adverse reactions
  - Development of resistant organisms
- Every time an antibiotic is prescribed
  - If at all possible, order recommended cultures before antibiotics are given
  - Make sure an indication, dose, and expected duration are part of the prescription order
  - Reassess within 48 hours and adjust antibiotic or discontinue if warranted
- Poor antibiotic usage affects ALL healthcare providers!
Resources

- Many!!
- Antimicrobial resistance and prudent prescribing
  - www.cdc.gov/drugresistance
  - www.cdc.gov/getsmart
  - www.cdc.gov/vitalsigns
  - The Sanford Guide to Antimicrobial Therapy 2017 47th edition
- Core Elements of Antibiotic Stewardship Programs
  - Hospital
  - Nursing Homes
  - Outpatient

Questions??

Melinda C. Joyce
joycmc@mchealth.net