Basics of Antibiotic resistance:
Focus on Carbapenem-resistant 
Enterobacteriaceae

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Provide exceptional compassionate clinical care that treats the whole person

• Strive to prevent problems and treat when necessary.
• Change Package Strategies and Prevent Healthcare Acquired Infections Change Bundle (Attachment 4):
**Presentation Objectives**

- Review common bacteria identified in nursing homes and antibiotics used to treat them
- Describe mechanisms for antibiotic resistance to develop in bacteria including carbapenem-resistance
- Discuss ways your laboratory can provide information about antibiotic resistance to your facility

**Basics on bacteria**

- Bacteria have different characteristics that allow us to identify them in the lab
  - Shape, size, gram stain, growth patterns, etc.
- We often use these characteristics to develop antibiotics
Common bacteria in healthcare

Gram positive
- Many are cocci, “round bacteria”
  - Examples are *Streptococci*, *Staphylococci*, *Enterococci*
  - *Clostridium difficile* (C. diff) is an anaerobic, Gram positive rod

Gram negative
- Most are bacilli, “rod-shaped bacteria”
  - Examples are: *E. coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Pseudomonas*, *Acinetobacter*

Important gram-negative bacteria

<table>
<thead>
<tr>
<th>Genus</th>
<th>Common species</th>
<th>Common culture sites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacteriacea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia</em> sp.</td>
<td><em>E. coli</em></td>
<td>Urine</td>
</tr>
<tr>
<td><em>Klebsiella</em> spp.</td>
<td><em>K. pneumoniae</em> and <em>K. oxytoca</em></td>
<td>Urine, resp.</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td><em>E. cloacae</em> and <em>E. aerogenes</em></td>
<td>Urine</td>
</tr>
<tr>
<td>Not Enterobacteriacea</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> sp.</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Urine, resp., wound</td>
</tr>
<tr>
<td><em>Acinetobacter</em> sp.</td>
<td><em>A. baumannii</em></td>
<td>Urine, resp.</td>
</tr>
</tbody>
</table>
Antibiotics 101

- Antibiotics are drugs that treat and kill bacteria
- They are grouped into classes based on their structure and activity
  - Narrow-spectrum target a few specific bacteria
  - Broad-spectrum can kill a wide variety of bacteria
- Antibiotic resistance = when the bacteria are no longer fully killed by the antibiotic
  - Bacteria with resistance can cause patients to have more severe infections which are harder and more costly to treat
  - Infection prevention programs track certain “bug-drug” combinations for resistance

Antibiotics: Beta Lactam classes

Penicillin, methicillin, amoxicillin and ampicillin
- Extended spectrum agents: piperacillin, ticarcillin
- Can be combined with a drug to help them overcome bacterial resistance
  - Amoxicillin + Clavulanate = Augmentin;
  - Ampicillin + Sulbactam = Unasyn
  - Piperacillin + tazobactam = Zosyn

Cephalosporins
- More gram positive activity: Cephalexin, Cefazolin
- More gram negative activity: Ceftriaxone, Ceftazidime, Cefepime
- New broader spectrum, including MRSA: Ceftaroline
Antibiotics: Carbapenems

- Extremely broad-spectrum, among the most powerful antibiotics we currently have available
- Spectrum includes *Streptococci*, susceptible *Staphylococci*, *Enterobactericeae*, *Pseudomonas*, *Acinetobacter sp.*., and anaerobic bacteria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>IV</td>
</tr>
<tr>
<td>Meropenem</td>
<td>IV</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>IM, IV</td>
</tr>
<tr>
<td>Doripenem</td>
<td>IV</td>
</tr>
</tbody>
</table>

Antibiotics: Gram positive agents

- **Vancomycin**
  - Treats methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Oral form is NOT absorbed from gut; only used to treat *Clostridium difficile*
  - IV form will get good systemic levels - used to treat all other infections
- **Daptomycin**
  - Covers resistant gram-positive organisms: MRSA and Vancomycin-resistant *Enterococci* (VRE)
  - Only available as IV formula
- **Linezolid**
  - Covers MRSA and VRE
  - Both oral and IV forms available and get good systemic levels
Antibiotics: Gram negative agents

Fluoroquinolones (oral and IV forms)
- Ciprofloxacin: Mostly gram negative activity
  - Commonly used for UTI treatment
- Levofloxacin/Moxifloxacin: Broader activity
  - Also used for treating UTIs and infections from gram-negative bacteria
  - Also covers *Streptococcus pneumoniae* and other respiratory bacteria

Aminoglycosides (only IV)
- Examples: Gentamicin, Tobramycin, Amikacin
- Excellent gram negative drugs – especially for urinary tract
- Limited use because of toxicity (kidney, hearing/balance)

Antibiotics: Miscellaneous

- Trimethoprim/Sulfamethoxazole (Bactrim):
  - Mainly given in oral form – must watch renal function
  - Considered narrow spectrum, but has activity against both Gram negative and Gram positive bacteria
  - Commonly used to treat UTIs
  - Also used for MRSA skin infections
- Azithromycin:
  - Commonly given in oral dose pack called “Z-pack”
  - Considered narrow spectrum, used for respiratory/sinus infections
- Metronidazole (Flagyl) (oral and IV form)
  - A primary treatment for *C. difficile* infections
  - Oral form can cause nausea and stomach upset
Understanding multidrug-resistance

- Multidrug-resistant organisms (MDROs) are a group of bacteria with important resistance patterns
- Sometimes just one key drug will define a MDRO
  - Methicillin-resistance in *Staphylococcus aureus*
  - Vancomycin-resistance in *Enterococcus* sp.
- Gram-negative bacteria can develop resistance to multiple classes of antibiotics
  - Resistance elements travel together so one bacteria can become resistant to many classes: Penicillins, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides
- Seen in *Enterobacteriaceae, Pseudomonas* and *Acinetobacter*

ABCs of MDROs

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Abbrev.</th>
<th>Antibiotic Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>MRSA</td>
<td>Methicillin-resistance</td>
</tr>
<tr>
<td><em>Enterococcus</em> (faecalis/faecium)</td>
<td>VRE</td>
<td>Vancomycin-resistance</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>ESBL</td>
<td>Extended spectrum penicillins and cephalosporin resistance</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>CRE</td>
<td>Carbapenem-resistance</td>
</tr>
<tr>
<td><em>Pseudomonas/Acinetobacter</em></td>
<td>MDR</td>
<td>Multiple drug-resistance</td>
</tr>
</tbody>
</table>
Mechanisms of antibiotic resistance

- Production of proteins that destroy antibiotics
  - Beta-lactamases
  - Cephalosporinases
  - Carbapenemases
- Change their cell structure
  - Blocks binding and function of antibiotics
- Reduce exposure
  - Pump antibiotics out
  - Increase cell barriers to block entry

Case scenario

- 70 year old admitted from hospital to nursing home
- Treated with Ceftriaxone for catheter-associated UTI x7 days before transfer
- Catheter still in place recently transferred
- Repeat urine culture ordered by MD prior to removing catheter
- Organism: E. coli, >10^5 cfu

<table>
<thead>
<tr>
<th>Drug</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Amp/Sulbactam</td>
<td>Resistant</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Resistant</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>Resistant</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Trimethoprim/Sulfa</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

http://bioinfo.bact.wisc.edu/themicrobialworld/bactresanti.html
**Penicillin and cephalosporin resistance in gram-negative bacteria**

- **Innate:** Resistance genes present in bacterial chromosomes (Example: AmpC)
  - Bacteria already had the capability to be resistant
  - Resistance was uncovered with overexpression of the gene
  - Consider in bugs like *Serratia, Pseudomonas, Acinetobacter*
- **Acquired:** Resistance genes entered bacteria through mobile genetic elements, called plasmids
  - Example: Extended spectrum Beta-lactamases (ESBLs)
  - Consider in *E. Coli, Klebsiella*
- Now we see both types of cephalosporin-resistance expressed in gram-negative bacteria

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**Case scenario #2**

- 70 year old admitted from hospital to nursing home
- Had complicated history including surgery, ICU care, ventilator-weaning
  - On transfer, has tracheostomy, PEG tube, urinary catheter and large sacral pressure ulcer
- MD sends culture from tracheostomy secretions
  - Organism: *Klebsiella pneumoniae*, >10^5 cfu

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<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Amp/Sulbactam</td>
<td>Resistant</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Resistant</td>
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Carbapenem-resistance in gram-negative bacteria

- Carbapenems are reserved for severe, complicated infections with multiple and often resistant bacteria
  - Recall: “Extremely broad-spectrum”
  - Resistance significantly limits treatment options for life-threatening infections
    - No new antibiotics in development for gram-negative bacteria
- Emerging resistance mechanisms can be spread
  - Carbapenemases are found on mobile genetic elements

Carbapenem-resistance: Mechanisms

- There are different ways that gram-negative bacteria become resistant to Carbapenems.
- Some bacteria have to make lots of changes to become resistant:
  - Step 1: Acquire or produce a cephalosporinase (to break down beta-lactam antibiotics)
  - Step 2: Lose a porin protein in the cell wall to prevent carbapenems from getting into the cell.
  - Step 3: Gain a pump to remove the carbapenem from the cell
- Others acquire resistance by a plasmid, which carries the genes for carbapenem resistance, “carbapenemases”
  - Examples include: KPC, NDM, VIM, OXA-48
Why focus on carbapenemases?

- The genetic material creating carbapenemases sits on highly mobile elements
  - These resistance elements can be shared between different bacteria very easily
  - Similar to concern with ESBL spreading cephalosporin-resistance
- Two carbapenemases getting lots of attention
  - *Klebsiella pneumoniae* carbapenemase (*KPC*)
  - New Delhi metallo-beta-lactamase (*NDM-1*)
- Identifying/containing bacteria which produce carbapenemase will *prevent the spread of resistance to other people and other organisms*

Microbiology 101: Identification

Growing the bacteria
- Traditional culture, use gram stain and biochemical reactions for identification
- Selective culture media (e.g., CHROMagar)

Examining parts of the bacteria
- Molecular diagnostic tests which identify specific fragments of DNA/RNA of organisms
  - Nucleic acid amplification tests (NAAT); Polymerase chain reaction (PCR)
- Matrix-assisted laser desorption/ionization (MALDI-TOF)
  - Very new technology: Uses mass spectrometry to identify bacteria based on weight and charge of ions
Microbiology 101: Susceptibility

Testing the growth in the presence of antibiotic
- Determining the minimum inhibitory concentration (MIC) – lowest amount of drug needed to stop growth
- Broth micro-dilution, Disk diffusion, E-test strips

Identifying resistance genes
- Molecular diagnostic tests – detect presence of specific resistance genes (NAAT, PCR)

Microbiology 101: Automated testing

- Systems with identification and susceptibility in one platform
  - Special growth panels contain biochemicals for identification and antibiotics for susceptibility testing
    - Bacteria of interest are inoculated onto panels and placed into system
  - Computer will identify organism and susceptibility interpretation
    - Uses pre-programmed algorithms based on growth patterns of bacteria on the panel
- Example systems (trade names): Microscan, Walkaway, VITEK 2, Phoenix, Sensititre
Can laboratories identify carbapenemases?

- Labs look for susceptibility to carbapenems by manual or automatic testing methods.

Challenges:
- Identification of carbapenem-resistance varies by which carbapenem is used for susceptibility testing.
- Low-levels of carbapenem resistance may not be detected by automated testing.
- Even if carbapenem resistance is detected – it may not mean the bacteria produce a carbapenemase.

Lab strategies to confirm carbapenemase production

- Modified Hodge test
  - Create a plate of susceptible E. coli
  - Place a Carbapenem disc in center
  - Negative control has clear zone of inhibition; zone gets distorted when carbapenemase is present.

- Molecular detection of resistance genes
  - Nucleic acid amplification tests (NAAT): Polymerase chain reaction (PCR)

What does it all mean?

- Microbiology labs may use different strategies for identifying carbapenem-resistance
  - Detection of carbapenemase production can vary by testing method being used
- Labs may NOT do the additional confirmatory testing to determine if resistance is from a carbapenemase
  - Requires additional knowledge, supplies/resources, time and technology
- Understanding the testing methods in your laboratory helps you interpret carbapenem-resistance reported in your facility
  - True burden may be over or under-estimated depending on testing methods and lab reporting

Starting the conversation with your lab

- Talk with the director of microbiology for your laboratory
  - Share your interest in understanding the carbapenem resistance in gram-negative bacteria identified in your facility
- Ask what methods are used for identification and antibiotic susceptibility
  - Is it an automated method?
  - Can they easily flag organisms with carbapenem-resistance?
- Ask whether they can perform “confirmatory” testing for carbapenemase-production (e.g., modified Hodge)
  - Could this be done if requested?
- Discuss a strategy for notifying your facility when a carbapenem-resistant bacteria is identified
Snapshot of resistance patterns: Facility antibiograms

- A yearly summary of the common bacteria from facility cultures and their susceptibility patterns to antibiotics
- Can be developed by your laboratory to show trends in resistance over time

Take Home Points

- Antibiotic resistance is a growing problem across all healthcare settings;
- Carbapenem resistance results in infections which cannot be treated with current antibiotics
- Understand the common bacteria causing infections among residents and the most frequently prescribed antibiotics in your facility
- The microbiology laboratory is a key partner in identifying and communicating when resistant organisms are isolated
Minnesota Resources

- Minnesota Antimicrobial Stewardship Program Toolkit for Long-Term Care Facilities:

  **Recommended nursing-driven core elements**
  - Identify a stewardship champion (i.e. Consider nursing leadership or IPs)
  - Identify a committee/team to incorporate stewardship (e.g. QA, infection control, nursing team meetings)
  - Measures antimicrobial use & regularly shares findings with all stakeholders (e.g. EMR, pharmacy records)
  - Incorporate relevant clinical guidelines (e.g. Loeb et al, SHEA, IDSA) into policies & protocols
  - Provide stewardship-related training to all healthcare personnel & empower all to recognize their role
  - Communicate stewardship-related messages to residents, families, & visitors
  - Develop clinical algorithms to cue appropriate diagnostic testing, antimicrobial timing, & review of results
  - Conduct infection surveillance that is rooted in resident signs and symptoms (e.g. 2012 Stone et al criteria)
  - Assess nursing process for 1) recognizing, 2) assessing, 3) communicating, and 4) documenting a resident’s change in condition
Minnesota Resources

Core Tools
• Action Steps and Strategies for Implementing Antimicrobial Stewardship
  • http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxb.pdf
• Antimicrobial Stewardship Gap Analysis Tool
  • http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxc.pdf
• Nursing and Provider Antibiotic Use Attitudes and Beliefs Survey
  • http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxd.pdf
• Antimicrobial Use Assessment
  • http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxe.pdf
• Nursing Process Evaluation Tool – Resident Change in Condition
  • http://www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/asp/ltc/apxf.pdf
• Supplemental Tools: Nursing communication tools, infection surveillance tools, clinical decision-making tools, education modules for nurses and nursing assistants, nursing skills fair questions, antimicrobial stewardship presentations, flyers, table tents, quizzes (see main page above)

Michigan and Wisconsin Resources

• Michigan Antibiotic resistance Reduction Coalition (MARR) Page:
  • http://mi-marr.org/
• Michigan Long-Term Toolkit:
  • http://mi-marr.org/LTC_toolkit.php
• Wisconsin Antibiotic Resistance Page:
  • https://www.dhs.wisconsin.gov/disease/aro.htm
• Wisconsin Healthcare-Associated Infections in Long-Term Care Coalition Resources (including stewardship)
  • https://www.dhs.wisconsin.gov/regulations/nh/ha-resource.htm
• Wisconsin Guidelines for Prevention and Control of Antibiotic Resistance Organisms in Health Care Settings:
National Resources from Centers from Disease Control and Prevention (CDC)

- All long-term care resources
  http://www.cdc.gov/longtermcare/index.html

- “The Core Elements of Antibiotic Stewardship for Nursing Homes”
  http://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html

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