Objectives

- Examine antibiotic resistance rates in hospitals and community
- Demonstrate association between antibiotic use and resistance
- Summarize clinical and laboratory tools for optimization of antibiotic utilization

Case #1

- A 65 year old man is admitted to the intensive care unit with fever, hypotension and altered mental status
- PHM: Rheumatoid arthritis s/p right total knee arthroplasty 3 years ago
- Vital signs: T 100.6, BP 80/55, PR 130, RR 28
- Exam: Right knee erythema, swelling, warmth and reduced range of motion
Case #1

- He received IV fluids and was started on vasopressors for BP support and O₂ face mask
- 2 sets of blood cultures were obtained
- IV vancomycin and piperacillin-tazobactam were started
- 12 hours later: Gram-positive cocci in clusters in blood
- 2 hours afterwards, multiplex PCR (Blood Culture Identification Panel) report:
  - Detection of *Staphylococcus* species and *Staphylococcus aureus*
  - MecA gene was not detected

Case #1

- However, primary team continued broad-spectrum antibiotics (IV vancomycin and piperacillin-tazobactam) awaiting final blood, urine & synovial fluid culture results
- On hospital day #2, he became hemodynamically stable and vasopressors were discontinued
- Same evening, he was taken to the operating room for irrigation, debridement and removal of right prosthetic knee with placement of antibiotic cement spacer

Case #1

- He received 2 units of blood following surgery
- He remained on IV fluids for maintenance
- Acetaminophen/hydrocodone was scheduled for pain
- On hospital day #3, serum creatinine increased to 4.3 mg/dL (compared to 1.5 mg/dL on admission)
- Eosinophils were not detected on spot urine sample
Case #1

In this patient with methicillin-susceptible *Staphylococcus aureus* bloodstream infection (BSI), acute kidney injury (AKI) could have been safely prevented by:

a) Avoiding post-operative narcotics
b) Delaying knee surgery until hospital day #5
c) Continuation of vasopressors for 48 hours following normalization of blood pressure
d) De-escalation of IV vancomycin and piperacillin-tazobactam to IV cefazolin on first day of admission
e) Early discharge from intensive care unit

Antibiotic-Associated Nephrotoxicity

- Historically, aminoglycosides were most commonly responsible, but current use is very low
- Penicillin derivatives (e.g. nafcillin) may rarely cause interstitial nephritis (low-grade fever, skin rash, urine eosinophilia)
- However, most commonly used nephrotoxic antibiotics:
  - IV Vancomycin monotherapy: 10% risk of AKI
  - IV Vancomycin and piperacillin-tazobactam combination: 33% risk of AKI

Vancomycin and Piperacillin-Tazobactam Nephrotoxicity

- Independent association with AKI
- Most common adverse event of this regimen
- Median time to nephrotoxicity is 3.5 days
- >80% of patients recover from AKI
- However, road to recovery is very long (2-3 weeks)
- Some may require hemodialysis prior to recovery
- Significant additional healthcare cost due to prolonged hospitalization, dialysis, etc.
Rapid Diagnostics

- Rapid diagnostic tests for microbial identification are taking antimicrobial therapy into new horizons
- Bacteria or yeast can be identified within hours of initial presentation
- Offers huge opportunities for optimization and early streamlining of antimicrobial therapy
- For bloodstream isolates:
  - MALDI-TOF: Matrix-assisted laser desorption/ionization time of flight
  - Blood Culture Identification Panel (multiplex PCR)

**BCID vs. MALDI-TOF**

<table>
<thead>
<tr>
<th>BCID Panel</th>
<th>MALDI-TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiplex PCR</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>Sample source: Blood, CSF, stool, upper respiratory tract</td>
<td>Sample source: Any (blood, sputum, urine, wound, etc.)</td>
</tr>
<tr>
<td>Identifies 27 targets, including 3 resistance genes</td>
<td>Identifies over 25,000 bacteria and fungi (no resistance gene detection)</td>
</tr>
<tr>
<td>Performed directly from blood sample once Gram stain reported as positive</td>
<td>Performed from subculture of blood isolate, requires some incubation time</td>
</tr>
<tr>
<td>Results within 2 hours of Gram stain report</td>
<td>Results nearly 24 hours after Gram stain</td>
</tr>
</tbody>
</table>

**Blood Culture Identification Panel (BCID)**

<table>
<thead>
<tr>
<th>Gram-Positive Bacteria</th>
<th>Gram-Negative Bacteria</th>
<th>Yeast</th>
<th>Antimicrobial Resistance Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>Escherichia coli</td>
<td>Candida glabrata</td>
<td>vanA/B - vancomycin resistance for Enterococcus spp.</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>Klebsiella pneumoniae</td>
<td>Candida krusei</td>
<td>KPC - carbapenem resistance (for Enterobacteriaceae)</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Klebsiella oxytoca</td>
<td>Candida parapsilosis</td>
<td></td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>Enterobacter cloacae</td>
<td>Candida tropicalis</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Proteus spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>Serratia marcescens</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acinetobacter baumannii</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemophilus influenzae</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neisseria meningitidis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case #2

- A 70 year old woman is admitted to the hospital with high fever with chills, headache, right lower abdominal pain, urinary frequency and dysuria
- PMH: Kidney transplantation 5 years ago on maintenance doses of prednisone and other antirejection medications
- No recent infections or antibiotic use
- Vital signs: T 102.6 F, BP 115/70, PR 115, RR 20
- Exam: tenderness in right lower quadrant, no neck stiffness

Case #2

- Labs: peripheral WBC count 16,000 (88% neutrophils), serum creatinine 1.3 mg/dL, normal liver enzymes, >180 WBCs on urinalysis
- Blood and urine cultures were obtained
- She was started empirically by primary team on IV vancomycin and cefepime
- Blood cultures Gram stain: gram-negative bacilli
- BCID detected *Enterobacteriaceae* and *Escherichia coli*
Case #2

She remains hemodynamically stable and off O₂. Optimal antimicrobial management at this point includes:

a) Continue both IV vancomycin & cefepime
b) D/C IV vancomycin, continue cefepime
c) D/C vancomycin, switch cefepime to ceftaxone
d) D/C IV vancomycin, switch cefepime to piperacillin-tazobactam
e) D/C IV vancomycin, switch cefepime to ertapenem

Bloodstream Antibiogram

<table>
<thead>
<tr>
<th>Gram Negative Organisms - Bloodstream Isolates - Palmetto Health</th>
<th>Number of Isolates</th>
<th>Amoxicillin/Clavulanate</th>
<th>Piperacillin/Tazobactam</th>
<th>Cefazolin</th>
<th>Ceftriaxone</th>
<th>Ceftazidime</th>
<th>Cefepime</th>
<th>Ertapenem</th>
<th>Meropenem</th>
<th>Gentamicin</th>
<th>Ciprofloxacin</th>
<th>SMZ/TMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacter species</td>
<td>18</td>
<td>92</td>
<td>83</td>
<td>81</td>
<td>100</td>
<td>75</td>
<td>105</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>100</td>
<td>95</td>
<td>79</td>
<td>86</td>
<td>87</td>
<td>87</td>
<td>96</td>
<td>100</td>
<td>95</td>
<td>76</td>
<td>81</td>
<td>95</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>47</td>
<td>96</td>
<td>87</td>
<td>96</td>
<td>90</td>
<td>90</td>
<td>95</td>
<td>100</td>
<td>86</td>
<td>91</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>13</td>
<td>92</td>
<td>77</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>17</td>
<td>98</td>
<td>82</td>
<td>74</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Prediction of ESBLs in Bloodstream Isolates

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>(95% CI)</th>
<th>p-value</th>
<th>Point allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient procedure within past 30 days</td>
<td>8.6</td>
<td>(3.0-22.5)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Prior infections or colonization with ESBLs</td>
<td>26.8</td>
<td>(7.0-108.2)</td>
<td>&lt;0.001</td>
<td>4</td>
</tr>
<tr>
<td>Number of BL/FQ courses within past 90 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>(reference)</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>6.3</td>
<td>(2.7-14.7)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>≥2</td>
<td>22.1</td>
<td>(8.6-57.2)</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
</tbody>
</table>

Augustine MR, et al. ICHE 2017
Two days later, *in vitro* antimicrobial susceptibility testing results of *E. coli* bloodstream and urinary isolates become available

- S: ampicillin, amoxicillin-clavulanic acid, cefazolin, ceftriaxone, cefepime, pip-tazo, ertapenem, ciprofloxacin, trimethoprim-sulfamethoxazole, doxycycline, nitrofurantoin
Patient continues to clinically improve (afebrile, reduced pain). However, she remains nauseated and not able to tolerate full diet. The best antimicrobial management at this point:

a) Continue IV ceftriaxone until she can be switched to an oral antibiotic 
b) D/C ceftriaxone, switch to IV ampicillin 
c) D/C ceftriaxone, switch to IV tigecycline 
d) D/C ceftriaxone, switch to nitrofurantoin 
e) D/C ceftriaxone, switch to fosfomycin

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**Case #2**

First assessment of antimicrobial therapy after bacterial identification (Gram stain, BCID, MALDI-TOF)

Second assessment of regimen after in vitro antimicrobial susceptibility results:

- Escalation: if isolate is not covered by antimicrobial regimen
- De-escalation to most effective, narrowest spectrum, safest, cheapest, single antimicrobial agent for treatment of that particular infection

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**Definitive Therapy of Gram-Negative BSI: De-escalation is key**

- First assessment of antimicrobial therapy after bacterial identification (Gram stain, BCID, MALDI-TOF)
- Second assessment of regimen after in vitro antimicrobial susceptibility results:
  - Escalation: if isolate is not covered by antimicrobial regimen
  - De-escalation to most effective, narrowest spectrum, safest, cheapest, single antimicrobial agent for treatment of that particular infection

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**Risks of Broad-Spectrum Antimicrobial Therapy**

- Nephrotoxicity
  - Median time to AKI following IV vancomycin and piperacillin-tazobactam combination is 3.5 days
- *Clostridium difficile* infection (CDI)
  - Median time to CDI following broad-spectrum therapy (anti-pseudomonal beta-lactams, carbapenems, etc.) is only 5 days
- Induction of antimicrobial resistance
  - >48 hours of antimicrobial therapy has been associated with significantly increased risk of antimicrobial resistance
Antimicrobial Resistance of *P. aeruginosa* Bloodstream Isolates

- **Pip-tazo**: 95% (Prior use of APBL), 92% (No prior use of APBL)
- **Ceftazidime**: 87% (Prior use of APBL), 85% (No prior use of APBL)
- **Cefepime**: 78% (Prior use of APBL), 77% (No prior use of APBL)
- **Meropenem**: 59% (Prior use of APBL), 54% (No prior use of APBL)

Troficanco C, et al. ASM Microbe 2016

National Trends of Antimicrobial Utilization, USA 2006-2012


Logan LK, et al. JPIDS 2016
National Trends of Antimicrobial Resistance: CRE

- Carbapenem-resistant Enterobacteriaceae (CRE) incidence rates are increasing nationally according to NNIS/NHSN
  - From 1.2% in 2001 to 4.2% in 2011
  - Most increase is among Klebsiella species (from 1.6% to 10.4% during same period)

MMWR 2013

Case #3

- A 76 year old woman with type 2 diabetes mellitus, complicated by chronic kidney disease
- She had a blister on her left plantar foot that progressed into chronic non-healing ulcer
- She was admitted to the hospital with left lower extremity cellulitis surrounding the superficial ulcer
- There was no purulence on exam to indicate I&D
- Blood cultures obtained on admission had no growth

Case #3

- She was empirically started on IV vancomycin and ciprofloxacin
- She had considerable clinical improvement after 5 days of hospitalization
- She was discharged home to finish a 14-day course of levofloxacin
Case #3

- She returns to the emergency room 5 days later with fever and watery diarrhea (8 times a day)
- No urinary frequency or dysuria
- Exam: resolution of left lower extremity cellulitis, mild left lower quadrant tenderness
- Peripheral WBC count 14,000, serum creatinine 2.7 mg/dL (baseline 2.3 mg/dL)
- Stool *C. difficile* PCR is positive
- Urinalysis: 12 WBCs and moderate leukocyte esterase

Case #3

The best antimicrobial management at this point is:

a) Continue levofloxacin, start oral metronidazole
b) D/C levofloxacin, start oral metronidazole
c) D/C levofloxacin, start oral metronidazole and vancomycin
d) D/C levofloxacin, start oral metronidazole and trimethoprim-sulfamethoxazole
e) D/C levofloxacin, start oral metronidazole and cephalexin

Case #3

- At primary care office follow up visit one week later, patient symptoms improved after treatment with oral metronidazole
- However, it was noted that urine culture obtained at the emergency room grew *E. coli* that was resistant to both ciprofloxacin and levofloxacin
- A prescription for oral cefdinir for 7 days was written for possible acute cystitis (no symptoms)
- Furosemide was also prescribed for bilateral lower extremity edema
Case #3

- Patient goes back to primary care office one month later for follow up
- Complaint of frequency of urination and nocturia since furosemide was started
- Urine culture was obtained which demonstrated this time an ESBL-producing *E. coli* that was resistant to all tested penicillins and cephalosporins
- It was also fluoroquinolone-resistant, but susceptible to trimethoprim-sulfamethoxazole, nitrofurantoin and fosfomycin

Case #3

The best antimicrobial strategy at this point is:

a) Treat with amoxicillin-clavulanic acid
b) Treat with fosfomycin
c) Treat with high dose trimethoprim-sulfamethoxazole, followed by low dose for chronic suppression
d) Treat with IV ertapenem through PICC, followed by nitrofurantoin chronic suppression
e) Keep off antibiotics for as long as possible and do not repeat urine cultures if asymptomatic

Case #3: Summary

- Gram-positive bacteria (staphylococci & streptococci) are by far the most common causes of cellulitis, including superficial diabetic foot ulcer infections
- Concomitant antibiotics in patients with CDI are independently associated with increased risk of recurrent CDI
- Risks of antimicrobial therapy, including induction of resistance, exceed any potential benefits in patients with asymptomatic bacteriuria

Fluoroquinolone Resistance in E. coli Bloodstream Isolates, Canada 2000-2010

Risk Factors for Fluoroquinolone Resistance, South Carolina

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence at skilled nursing facility</td>
<td>2.3 (1.4-3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient GI/GU procedure within 1 month</td>
<td>3.7 (2.0-6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior fluoroquinolone use within 6 months</td>
<td>1</td>
<td>(reference)</td>
</tr>
<tr>
<td>Within 3 months</td>
<td>7.9 (4.5-13.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Within 3-6 months</td>
<td>2.8 (1.2-6.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
**Risk Factors for Fluoroquinolone Resistance, North Carolina**

**Parameter** | **OR (95% CI)**
---|---
Hospital-acquired infection | 0.19 (0.05-0.69)**
Presence of urinary catheter | 2.7 (0.97-7.6)
Presence of central line | 4.8 (1.1-18.0)**
Receipt of mechanical ventilation | ***
Receipt of immunosuppressive therapy | ***
Receipt of antibiotics within prior 90 days | 3.1 (1.2-8.1)**
Admission to hospital within last 90 days | ***
Admission from skilled nursing facility or long-term care facility | 5.5 (1.5-18.0)**

Koliscak LP, et al. AAC 2013

**Fluoroquinolone Susceptibility: Hospitals vs. Community**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Community-acquired</th>
<th>Healthcare-associated</th>
<th>Hospital-acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>39</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>70</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>80</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>83</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>79</td>
<td>75</td>
<td>76</td>
</tr>
</tbody>
</table>


**ESBL-Producing E. coli, Canada 2006-2015**

Mineau S, et al. ASM Microbe 2017
Community-Onset ESBL E. coli

Risk Factors for ESBL-Producing Bacteria

<table>
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</tbody>
</table>

Figure 2: Ambulatory Antibiotic Prescription, USA 2010

The frequency with which doctors prescribe antibiotics varies greatly from state to state. The reasons for this variation are being studied and might suggest areas where improvements in antibiotic prescribing (these unnecessary prescriptions) would be most helpful.

CDC, 2010
Antibiotic Use and Resistance

- There is a strong and consistent association between prior antibiotic use and resistance
  - In both community- and hospital-onset bacteria
  - Applicable to various classes of antibiotics
  - Antibiotic effect on microbiome may last for several months

- The best way to slow down the rapid increase in antimicrobial resistance rates is to use antibiotics wisely both in hospitals and in the community

Thank You