Optimizing Selection of Empirical Antimicrobial Therapy in the Era of Precision Medicine

Majdi Al-Hasan, MBBS
Associate Professor of Medicine
University of South Carolina School of Medicine
Disclosure

• I have no potential conflicts of interest relevant to this presentation.
Objectives

• Discuss benefits of appropriate empirical antimicrobial therapy in patients with serious infections
• Review risks of non-stratified use of broad-spectrum antimicrobial agents
• Demonstrate role of prior antimicrobial use among other patient-specific risk factors for antimicrobial resistance
• Utilize clinical tools for prediction of antimicrobial resistance in decision-making of empirical therapy
Appropriate Empirical Antimicrobial Therapy Saves Lives of Critically Ill Patients with BSI

Cain SE, et al. AAC 2015

NNT=3
Shorter Hospitalization with Appropriate Empirical Antimicrobial Therapy

Battle SE, et al. JAC 2017
Benefits of Appropriate Empirical Antimicrobial Therapy

- Improved survival in patients with sepsis (qSOFA $\geq 2$)
- Shorter hospital length of stay
- Faster resolution of symptoms
- Reduction in risk of complications
Change in Antibiotic Utilization in USA Hospitals, 2006-2012


National Trends of Antimicrobial Resistance: CRE

- Carbapenem-resistant *Enterobacteriaceae* (CRE) incidence rates are increasing nationally
  - 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)
Case #1

• A 48-year old lady presents to emergency room with high fever and right upper abdominal pain
• No recent hospitalizations, procedures, or antimicrobial use
• Vital signs: T 39.2 C, BP 125/75, HR 115, RR 20
• Exam: Jaundice, right upper quadrant abdominal tenderness
Case #1

• Labs:
  – CBC: Leukocytosis (WBC 17,000; 86% neutrophils)
  – CMP: high total and direct bilirubin, high alkaline phosphatase

• Imaging:
  – RUQ ultrasound: dilated common bile duct with no retained biliary stones

• Microbiology:
  – Blood cultures on admission grew gram-negative bacilli
Case #1

The most appropriate empirical antimicrobial regimen for treatment of acute cholangitis in this patient is:

a) Ampicillin-sulbactam
b) Cefepime and metronidazole
c) Ceftriaxone and metronidazole
d) Ertapenem
e) Piperacillin-tazobactam
Acute Cholangitis

• *Escherichia coli* is the most common gram-negative bacteria causing community-onset acute cholangitis, followed by *Klebsiella* species

• Viridans group streptococci and anaerobes (*Bacteroides fragilis*, etc.) are also common

• *Pseudomonas aeruginosa* is unlikely except in special hosts
Risk Factors for Bloodstream Infections due to *Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Immune compromised host</td>
<td>3.7 (2.0-6.7)</td>
<td>&lt;0.001</td>
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<td>Current hospitalization for &gt;5 days</td>
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Hammer KL, et al. *DMID* 2017
Pseudomonas aeruginosa
Risk Score

Hammer KL, et al. DMID 2017
Pseudomonas aeruginosa Risk Score

Hammer KL, et al. DMID 2017
Optimizing Empirical Antimicrobial Therapy for Enterobacteriaceae

• Bloodstream isolate was identified as *Escherichia coli* by multiplex PCR, Blood Culture Identification Panel (BCID)

• Increasing antimicrobial resistance rates of *E. coli* and other *Enterobacteriaceae* isolates complicates antimicrobial management

• Tools to improve empirical antimicrobial therapy?
  – National antimicrobial resistance rates?
  – Hospital (institutional) antibiogram?
  – Patient-specific antibiogram?
Antimicrobial Resistance of *E. coli* Bloodstream Isolates, USA 1998-2007

![Graph showing antimicrobial resistance trends from 1998-2007 for Ampicillin, Ampicillin/sulbactam, SXT, and Ciprofloxacin.](image-url)

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

## Hospital Antibiogram

### Gram-Negative Bacteria

**All Source Isolates**

**Palmetto Health**

<table>
<thead>
<tr>
<th>Number of Isolates</th>
<th>Ampicillin</th>
<th>Amoxicillin/clavulanate</th>
<th>Piperacillin/tazobactam</th>
<th>Cefazolin</th>
<th>Ceftriaxone</th>
<th>Cefazidime</th>
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<th>Cefepime</th>
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<td>87</td>
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<td>89</td>
<td>84</td>
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<tr>
<td><strong>Escherichia coli</strong></td>
<td>1438</td>
<td>47</td>
<td>75</td>
<td>95</td>
<td>76</td>
<td>90</td>
<td>90</td>
<td>94</td>
<td>99</td>
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<td>69</td>
<td>75</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>551</td>
<td></td>
<td>95</td>
<td>88</td>
<td>82</td>
<td>86</td>
<td>86</td>
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</tr>
<tr>
<td><strong>Proteus mirabilis</strong></td>
<td>275</td>
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<td>98</td>
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<td>80</td>
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<td>86</td>
<td>92</td>
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<td>71</td>
<td></td>
</tr>
</tbody>
</table>
Precision Medicine

• “Precision or individualized medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in environment, lifestyle and genes for each person”

National Institute of Health, Precision Medicine Initiative
Precision Medicine

• There is no better example of precision medicine than selection of empirical antimicrobial therapy in patients with serious bacterial infections.

• Risk of antimicrobial resistance varies widely from one individual to another based on:
  – Prior use of antimicrobial agents
  – Other healthcare exposures

*Palmetto Health Antimicrobial Stewardship and Support Team, Palmetto Health Antimicrobial Guidebook 2017*
Prediction of Antimicrobial Resistance

• “Prediction of antimicrobial resistance opens a new horizon in the selection of empirical antimicrobial therapy”

• “It allows healthcare providers to initiate therapy based on patient-specific risk of antimicrobial resistance, rather than average antimicrobial resistance rates from large multi-national, nationwide, regional or local surveillance, population-based, or institutional data”

Dan S, et al. AAC 2016; 60: 2265-72
# Risk Factors for ESBL-producing *Enterobacteriaceae* in Bloodstream Isolates

Augustine MR, et al. *ICHE* 2017

<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 GI/GU 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/colonization with ESBLs within 12 months</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>
ESBL Prediction Score

Augustine MR, et al. ICHE 2017
ESBL Prediction Score

Augustine MR, et al. ICHE 2017
## Case #1: Generic vs. Patient-Specific Antibiograms

<table>
<thead>
<tr>
<th></th>
<th>Amoxicillin</th>
<th>Amoxicillin/clavulanate</th>
<th>Ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eshcerichia coli</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic Antibiotic</td>
<td>47</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Patient-Specific Antibiotic</td>
<td>83</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>
Predictable vs. Unpredictable Antimicrobial Resistance

- Resistance to amoxicillin and amoxicillin-clavulanic acid in *E. coli* isolates cannot be reliably predicted due to:
  - Frequent use in community
  - Widespread use in children and adults
  - Combination of high prevalence and high probability of household transmission of TEM-1 producing *E. coli*
Case #1B

- Two days later, in vitro antimicrobial susceptibility testing results of E. coli bloodstream isolate become available
- R: Ampicillin
- S: Amoxicillin-clavulanic acid, cefazolin, ceftriaxone, cefepime, piperacillin-tazobactam, ertapenem, ciprofloxacin, trimethoprim-sulfamethoxazole, doxycycline
Case #1B

Patient continues to clinically improve (afebrile, reduced pain). However, he remains nauseated and not able to tolerate full diet. The best antimicrobial management at this point:

a) Continue IV ceftriaxone and metronidazole until he can be switched to an oral antibiotic
b) D/C ceftriaxone and metronidazole, switch to IV ampicillin-sulbactam
c) D/C ceftriaxone and metronidazole, switch to IV tigecycline
d) D/C antimicrobial therapy at this point since he is afebrile
Antimicrobial Therapy: De-escalation is Key

• Optimization of empirical therapy based on patient-specific risk factors for antimicrobial resistance

• Reassessment of antimicrobial regimen after bacterial identification (Gram stain, multiplex PCR, MALDI-TOF)

• De-escalation if empirical regimen is too broad
  – Discontinue IV vancomycin in absence of gram-positive bacteria
  – Discontinue antipseudomonal β-lactams (APBL) in absence of *Pseudomonas aeruginosa*
De-Escalation off Anti-Pseudomonal Beta-Lactams (APBL)

Bookstaver PB, et al. AAC 2017

Pre-intervention
Phase 1
Phase 2

P<0.001
Antimicrobial Therapy: De-escalation is Key

• Second assessment after in vitro antimicrobial susceptibility testing results:
  – Escalation: if isolate is not susceptible to empirical agent
  – De-escalation to most effective, narrowest spectrum, safest, cheapest, single antimicrobial agent for treatment of that particular infection
Risks of Broad-Spectrum Antimicrobial Therapy

- **Nephrotoxicity**
  - Median time to acute kidney injury following IV vancomycin and piperacillin-tazobactam is 3.5 days

- **Clostridium difficile infection (CDI)**
  - Median time to CDI following broad-spectrum therapy (anti-pseudomonal penicillins, cephalosporins, carbapenems, fluoroquinolones, etc.) is only 5 days

- **Induction of antimicrobial resistance**
  - >48 hours of antimicrobial therapy is associated with significantly increased risk of antimicrobial resistance
Case #2

- A 55 year old gentleman with squamous cell lung cancer s/p several cycles of chemotherapy
- He was admitted to hospital for salvage chemotherapy through a peripheral IV
- On hospital day #10, he developed fever and was feeling unwell
- Vitals: T 102.0 F, BP 130/85, HR 130, RR 18
- Exam: conjunctival pallor, mucositis, otherwise unremarkable
Case #2

• Labs: WBC 900, absolute neutrophil count 280, Hct 27, platelets 55
• CXR: No new infiltrates
• Blood and urine cultures were obtained
• History of penicillin allergy at age of 4 years (non-specific maculopapular rash on trunk and both arms)
• Recent antibiotics include course of levofloxacin 6 weeks ago for possible pneumonia
• No known colonization with antimicrobial resistant bacteria
Case #2

The best empirical antimicrobial regimen for neutropenic fever in this patient while awaiting culture results include:

a) Aztreonam  
b) Ceftazidime  
c) Cefepime  
d) Ciprofloxacin and vancomycin  
e) Meropenem and vancomycin
### Risk Factors for Bloodstream Infections due to *Pseudomonas aeruginosa*

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Hammer KL, et al. *DMID* 2017
**Pseudomonas aeruginosa**

**Risk Score**

Hammer KL, et al. *DMID* 2017
Antipseudomonal Therapy

- Neutropenia is the strongest risk factor for systemic infections due to *Pseudomonas aeruginosa*

- Ceftazidime has reliable antipseudomonal coverage, but poor gram-positive activity (streptococci, etc.)

- Similarly, aztreonam and ciprofloxacin are (for the most part) strictly gram-negative agents

- Monotherapy with ceftazidime, aztreonam or ciprofloxacin should not be used for empirical therapy of neutropenic fever
Antipseudomonal Therapy

• Is empirical IV vancomycin and ciprofloxacin an option?
  – Hypothetically yes since it may cover gram-positive (vancomycin) and gram-negative bacteria (ciprofloxacin)
  – However, increasing antimicrobial resistance rates to fluoroquinolones makes it less reliable
  – Recent use of fluoroquinolones (levofloxacin) in this patient makes this regimen practically inadequate
## Major Risk Factors for Fluoroquinolone Resistance

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds ratio</th>
<th>(95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residence at skilled nursing facility</td>
<td>2.3</td>
<td>(1.4-3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Outpatient GI/GU procedure within 1 month</td>
<td>3.7</td>
<td>(2.0-6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior fluoroquinolone use within 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>(reference)</td>
<td></td>
</tr>
<tr>
<td>Within 3 months</td>
<td>7.9</td>
<td>(4.5-13.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Within 3-12 months</td>
<td>2.8</td>
<td>(1.2-6.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

# Fluoroquinolone Resistance Score

## Risk Factors for Fluoroquinolone Resistance

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Point Allocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1</td>
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<tr>
<td>Residence in a skilled nursing facility</td>
<td>2</td>
</tr>
<tr>
<td>Outpatient GI/GU procedure within past 30 days</td>
<td>3</td>
</tr>
<tr>
<td>Prior fluoroquinolone use within past 12 months</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Within 3 months</td>
<td>5</td>
</tr>
<tr>
<td>Within 3-12 months</td>
<td>3</td>
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</table>

Fluoroquinolone Resistance Score

Antipseudomonal Therapy

• What about IV vancomycin and meropenem?
  – Meropenem provides broad-spectrum coverage, including *P. aeruginosa*
  – However, meropenem use seems excessive in absence of prior beta-lactam use or colonization with resistant bacteria
  – Moreover, IV vancomycin is not indicated in patients with neutropenic fever in absence of sepsis (qSOFA ≥2) or clinical suspicion of central line or skin and soft tissue infections
Penicillin Allergy

• Cross-reactivity between penicillins and late-generation cephalosporins ($2^{nd}$, $3^{rd}$, $4^{th}$, etc.) is low (<3%)

• Cross-reactivity between penicillins and carbapenems is comparable to that between penicillins and cephalosporins

• In patients with minor penicillin reactions, benefits of treating serious infections with cephalosporins exceed potential risks

## Combination Therapy for *P. aeruginosa*?

<table>
<thead>
<tr>
<th>Gram-Negative Bacteria</th>
<th>Number of Isolates</th>
<th>Ampicillin</th>
<th>Amoxicillin/clavulanate</th>
<th>Piperacillin/tazobactam</th>
<th>Cefazolin</th>
<th>Ceftriaxone</th>
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<th>Ceftepime</th>
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<td>90</td>
<td>69</td>
<td>75</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>551</td>
<td>95</td>
<td>82</td>
<td>86</td>
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</table>
Combination Therapy for *P. aeruginosa*?

- According to generic antibiogram, APBL provide adequate coverage for only 84-87% of *P. aeruginosa* isolates
- These susceptibility results are consistent with most other hospitals in Southeastern USA
- Mid-80’s coverage is not accepted by clinical standards in immune compromised or critically-ill patients
- Such low-quality data provided in antibiograms encourage non-stratified use of combination therapy
Prediction of β-lactam resistance in *P. aeruginosa* Bloodstream Isolates

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior β-lactams</td>
<td>1</td>
<td>Reference</td>
</tr>
<tr>
<td>Prior β-lactams within 30 days</td>
<td>5.3 (2.2-12.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior β-lactams within 31-90 days</td>
<td>0.8 (0.1-4.5)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Antimicrobial Resistance of *P. aeruginosa* Bloodstream Isolates

![Bar Chart]

- **Pip-tazo**
  - Prior use of APBL: 78%
  - No prior use of APBL: 92%

- **Ceftazidime**
  - Prior use of APBL: 78%
  - No prior use of APBL: 95%

- **Cefepime**
  - Prior use of APBL: 83%
  - No prior use of APBL: 96%

- **Meropenem**
  - Prior use of APBL: 77%
  - No prior use of APBL: 94%

Trofican C, et al. ASM Microbe 2016
# Case #2: Generic vs. Patient-Specific Antibiograms

<table>
<thead>
<tr>
<th>Pseudomonas aeruginosa</th>
<th>Piperacillin/tazobactam</th>
<th>Ceftazidime</th>
<th>Cefepime</th>
<th>Meropenem</th>
<th>Ciprofloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Antibiogram</strong></td>
<td>87</td>
<td>85</td>
<td>84</td>
<td>86</td>
<td>71</td>
</tr>
<tr>
<td><strong>Patient-Specific Antibiogram</strong></td>
<td>92</td>
<td>95</td>
<td>96</td>
<td>94</td>
<td>26</td>
</tr>
</tbody>
</table>
Case #2

- Patient clinically improved after 3 days of IV cefepime with relative decline in temperature curve

- Blood cultures grew *Klebsiella pneumoniae*
  - R: ampicillin, amoxicillin-clavulanic acid, cefazolin, ciprofloxacin, trimethoprim-sulfamethoxazole
  - S: ceftriaxone, cefepime, piperacillin-tazobactam, ertapenem, meropenem, tobramycin, doxycycline
Case #2

The best antimicrobial management at this point is:

a) Continue cefepime
b) Continue cefepime, add IV tobramycin
c) Discontinue cefepime, switch to ertapenem
d) Discontinue cefepime, switch to tigecycline
e) Discontinue cefepime, switch to ceftriaxone
Summary

• Selection of empirical antimicrobial therapy should be based on patient-specific risk factors for antimicrobial resistance

• Over-estimation of antimicrobial resistance risk results in unnecessarily excessive use of antimicrobial agents and further increase in antimicrobial resistance among individuals and within hospitals
Summary

• There is a strong and consistent association between prior antimicrobial use and resistance
  – In both community- and hospital-onset bacteria
  – Applicable to various classes of antimicrobials
  – Antimicrobial effect on microbiome may last for several months

• Best way to slow down rapid increase in antimicrobial resistance is to use antibiotics wisely both in hospitals and community
Thank You

CE Evaluation Access Code

H84