Think, Act, and Respond

Part 1

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Course of the Talk

- Background information
- Brief review of the various classes of antibiotics highlighting important aspects of the included Abx
- The relationship of MIC to antibiotic selection
- Pitfalls when interpreting MIC information
- Focus on multidrug resistant organisms
  - MRSA
  - VRE
  - Pseudomonas
  - ESBL
How Bacteria Regard us
Workup

- Prior to initiation of therapy for a suspected infection, a differential diagnosis with suspected organism(s) should be considered
  - The site of infection
  - History of antibiotic use
  - Co-morbidities
  - Common pathogens in the community/setting
  - Local resistance rates to various antibiotics
Once an organism(s) is/are suspected, antibiotic selection should be based on the following:

- Suspected organism(s) and antibiotic coverage
- PKPD of the antibiotic
  - Optimal parameters for eradication of the organism (PD)
  - Optimal parameters for reaching the organism (PK)
- Resistance rates of the organism(s) to the considered abx(s)
- Laboratory data
- Concomitant medications
MRSA
Empiric Antibiotic Selection

MRSA

- Considered a culprit in most SSTI, HAP, and CA-necrotizing pneumonia
- Often SSTI MRSA is misdiagnosed as spider bites
- Draining the abscess is of greater clinical importance than antibiotic use
  - Cure rate from I&D alone is ~85% for CA-MRSA SSTI
- If necrotizing MRSA infection is suspected, immediate therapy with clindamycin or linezolid or both is/are warranted (vancomycin may be used in combination with either agent)
Empiric Antibiotic Selection
MRSA

<table>
<thead>
<tr>
<th>JAN TO DEC 2010</th>
<th>*</th>
<th>Clindamycin</th>
<th>Trimeth/Sulfa</th>
<th>Vancomycin</th>
<th>Tetracycline</th>
<th>Tigecycline</th>
<th>Linezolid</th>
<th>Synercid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self Regional Healthcare % Susceptible Gram Positive Isolates</td>
<td>No. Isolates</td>
<td>77</td>
<td>97</td>
<td>92</td>
<td>100</td>
<td>-</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>Staph aureus</td>
<td>1188</td>
<td>76</td>
<td>97</td>
<td>94</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>95</td>
</tr>
<tr>
<td>Staph aureus MRSA</td>
<td>637</td>
<td>77</td>
<td>97</td>
<td>94</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>95</td>
</tr>
<tr>
<td>Staph aureus MSSA</td>
<td>551</td>
<td>78</td>
<td>98</td>
<td>91</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>659</td>
<td>93</td>
<td>95</td>
<td>73</td>
<td>-</td>
<td>-</td>
<td>72</td>
<td>94</td>
</tr>
<tr>
<td>coag neg Staph</td>
<td>340</td>
<td>58</td>
<td>99</td>
<td>51</td>
<td>82</td>
<td>100</td>
<td>98</td>
<td>50</td>
</tr>
<tr>
<td>Gp B Strep</td>
<td>151</td>
<td>44</td>
<td>100</td>
<td>99</td>
<td>14</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*number of isolates may vary with each antimicrobial

<table>
<thead>
<tr>
<th>Resistance</th>
<th>%</th>
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<tbody>
<tr>
<td>MRSA</td>
<td>54%</td>
</tr>
<tr>
<td>VRE</td>
<td>5%</td>
</tr>
<tr>
<td>PRSP (including screens)</td>
<td>51%</td>
</tr>
<tr>
<td>H flu (BLP)</td>
<td>24%</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Pros</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Linezolid (Zyvox®)</td>
<td>MRSA toxin specific, Severe SSTI, step-down therapy for vancomycin</td>
</tr>
<tr>
<td>Clindamycin (Cleocin®)</td>
<td>No monitoring required, Anaerobic coverage, MRSA toxin specific</td>
</tr>
<tr>
<td>TMP-SMX (Bactrim®)</td>
<td>Low cost, limited ADR, step-down therapy, Good for UTI</td>
</tr>
<tr>
<td>Doxycycline/Minocycline</td>
<td>Low cost, good renal penetration, limited ADR</td>
</tr>
</tbody>
</table>

*Erythromycin induced Clindamycin resistance (next slide)
**Based on sensitivity to tetracycline on antibiogram
D-Test (Erythromycin Induced Clindamycin Resistance)
# Empiric Antibiotic Selection (IV)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin (gold standard)</td>
<td>Bacterioidal, cheap, well studied, gold standard</td>
<td>Monitoring trough conc, PK variability, renal toxicity (1% with monotherapy)</td>
</tr>
<tr>
<td>Linezolid (Zyvox®)</td>
<td>PO and IV, no renal dose adjustments</td>
<td>Bacteriostatic, inferior to vanco for bacteremia &amp; CLBI &amp; UTI Thrombocytopenia (CBC q week) Interaction with SSRI/TCA</td>
</tr>
<tr>
<td>Daptomycin (Cubicin®)</td>
<td>Bacterioidal, lack of interactions, good for bacteremia and UTI</td>
<td>Elevated CK (baseline + q week) Do not use in PNA! <strong>vancomycin resistance</strong></td>
</tr>
<tr>
<td>Tigecycline (Tigycil®)</td>
<td>Broad GN coverage, anaerobic coverage</td>
<td>Blackbox warning for bacteremia Bacteriostatic, Collateral damage</td>
</tr>
<tr>
<td>Ceftaroline</td>
<td>Non-inferior to vanco for SSTI No monitoring</td>
<td>No data on PNA Renal dosage adjustments Very limited clinical data to date</td>
</tr>
<tr>
<td>Q-D Synercid®</td>
<td>Limited resistance</td>
<td>Bacteriostatic, common GI ADR, limited clinical utility</td>
</tr>
<tr>
<td>Telavancin (Vibativ®)</td>
<td>Non-inferior to vancomycin for MRSA SSTI</td>
<td>Not studied in CAP/HAP.</td>
</tr>
</tbody>
</table>
Enterococcus are facultatively anaerobic
Consists of E. faecium and E. faecalis
- E. faecium is associated with VRE (30:1 vs E. faecalis)
Most commonly encountered with UTI
High incidence of endocarditis if Enterococcus bacteremia detected
Bacteremia associated with central venous catheter
Empiric Antibiotic Selection
Enterococcus

Based on SRH antibiogram no reason to suspect VRE over VSE
Empiric Antibiotic Selection

Enterococcus

- Remove catheter if present prior to starting abx
- For the treatment of UTI/Intra-abdominal/wound:
  - PCN
  - Ampicillin/Amoxicillin (Drug of choice)
  - Levofloxacin (high resistance)
  - Vancomycin (alternative to APCN in PCN allergic pts)
- For serious infections (bacteremia, endocarditis, CRBI)
  - \textit{Gentamicin + vancomycin (synergy)}
    - If proven to be sensitive to ampicillin then change to ampicillin+gentamicin. If proven to be vancomycin resistant, use daptomycin or linezolid
Empiric Antibiotic Selection

VRE

- Often associated with UTI or catheter related bloodstream infection
- Bacteremia associated with endocarditis
- VRE due to *E. faecium* >>> *E. facalis* (30:1)
- VRE in the stool has very limited clinical significance and is usually considered colonization and not treated
Empiric Antibiotic Selection

VRE

- **VRE UTI/SSTI:**
  - Daptomycin (drug of choice)
    - 4-6mg/Kg/dose
  - Linezolid (alternative for UTI but good for SSTI)
  - Tigecycline (alternative for SSTI)
  - Fosfomycin (1 dose) – for UTI only
  - Nitrofurantoin - for UTI only
  - Telavancin (not all VRE isolates)

- **VRE bacteremia/CRBSI/Endocarditis**
  - Daptomycin (drug of choice)
    - 8-10mg/Kg/day
    - Request microbiology to test sample against daptomycin
  - Synercid (only if E. faecium) – bacteriostatic
  - Linezolid – NOT RECOMMENDED
  - Tigecycline – NOT RECOMMENDED
Pseudomonas aeruginosa
Empiric Antibiotic Selection
Pseudomonas

- Most common in residents of NH or recent hospitalizations
- History of recent antibiotic use (within past 3 months)
- Current or past admission to ICU setting
- Patients with chronic indwelling catheters
- Patients with history of COPD
- Patients with recurrent UTIs
- Diabetic patients
- Intravenous drug users
- History of recurrent infections (UTI, DFI, GI)
Empiric Antibiotic Selection

Pseudomonas

- Consider pseudomonas as suspect in:
  - HAP
  - Recurrent UTI with history of FQ use
  - Patients in ICU setting
  - Diabetic SSTI
  - SSTI with signs of pseudomonas infection
Note lowest susceptibility to FQ due to overuse
Note resistance to Zosyn and Cefepime is approaching 10%
Note 4% of pseudomonas is resistant to imipenem-cilastin
Empiric Antibiotic Selection

Pseudomonas

- **UTI/SSTI:**
  - Ciprofloxacin (oral option), Levofloxacin (oral option)
  - Gentamicin (IV)
  - Zosyn (IV)
  - Cefepime (IV)
  - Ceftazidime (IV)
  - Carbapenems (not including Ertapenem)

- **PNA/Bacteremia:**
  - **Antipseudomonal Beta-lactamse Inhibitor OR**
  - **Gentamicin/tobramycin PLUS**
    - Levofloxacin
    - Zosyn
    - Cefepime
    - Ceftazidime
    - Carbapenems
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pros</th>
<th>Cons</th>
<th>SRH 2010 Antibiogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Oral, good urinary penetration</td>
<td>High resistance, drug interactions</td>
<td>74%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Oral, good urinary penetration,</td>
<td>High resistance, PMC, unnecessary coverage</td>
<td>71%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Mortality benefit w/ PNA, Good urinary penetration, Cost</td>
<td>Monitoring required, Renal toxicity, ototoxicity</td>
<td>89%</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Narrower coverage, no monitoring, Good urinary penetration</td>
<td>Cause of ESBL resistance, Development of resistance is often rapid,</td>
<td>91%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>No monitoring, less PMC, broad spectrum if PNA &amp; UTI or bacteremia</td>
<td>Broad spectrum and increasing resistance</td>
<td>92%</td>
</tr>
<tr>
<td>Imipenem-cilastin</td>
<td>Broad spectrum, least resistance, effective against ESBL</td>
<td>Seizure risk, needs to be reserved for ESBL</td>
<td>96%</td>
</tr>
<tr>
<td>Pipercillin- Tazobactam</td>
<td>Broad spectrum including anaerobes</td>
<td>Dosed based on indication and bug</td>
<td>92%</td>
</tr>
</tbody>
</table>
Although quinolones can penetrate into the lung better than aminoglycosides and have less potential for nephrotoxicity, a trend toward improved survival has been seen with aminoglycoside-containing, but not with quinolone-containing, combinations (259). In some studies, combination therapy has been continued for less than the full course of therapy, with discontinuation of the aminoglycoside after 5 days if the patient is improving (235).
Pseudomonas/VAP Study

Variability in Antibiotic Prescribing Patterns and Outcomes in Patients With Clinically Suspected Ventilator-Associated Pneumonia*

Robert A. Fowler, MD, MS; Kara E. Flavin, BA; Juliana Barr, MD; Ann B. Weinacker, MD, FCCP; Julie Parsonnet, MD; and Michael K. Gould, MD, MS, FCCP

Chest 2003;123;835-844
DOI 10.1378/chest.123.3.835
**Table 4—Cox Regression Analysis for In-hospital Survival**

<table>
<thead>
<tr>
<th>Clinical Predictors</th>
<th>No. (%)</th>
<th>HR of Death (95% CI)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Specific antibiotic therapy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antipseudomonal penicillins plus</td>
<td>96 (62.2)</td>
<td>0.41 (0.21–0.80)</td>
<td>0.009</td>
</tr>
<tr>
<td>β-Lactamase inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>35 (22.7)</td>
<td>0.43 (0.16–1.11)</td>
<td>0.08</td>
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<td>77 (50)</td>
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<td>Monotherapy vs combination therapy</td>
<td>72 (46.8)</td>
<td>1.19 (0.58–2.42)</td>
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<td>Inappropriate antibiotic therapy</td>
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<td>Other clinical predictors*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>36 (23.4)</td>
<td>4.06 (1.82–9.07)</td>
<td>&lt;0.001</td>
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<tr>
<td>Immunocompromised state</td>
<td>61 (39.6)</td>
<td>2.68 (1.21–5.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>154 (100)</td>
<td>1.12 (1.04–1.20)</td>
<td>0.002</td>
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*Clinical variables included in the multivariable model but not associated with survival included age, gender, medical vs surgical diagnosis, length of ICU and hospital stay prior to VAP, trauma, witnessed aspiration, chronic respiratory disease, ARDS, tracheostomy, cardiac disease, shock, neurologic disease, malignancy, malnutrition, renal failure, bacteremia, tracheal colonization with multidrug resistant bacteria, antibiotic treatment within 10 days prior to VAP, treatment with histamine type-2 blockers, and treatment with neuromuscular blockers.
Interpreting the Results

• What is the difference between hazard ratio (HR) and relative risk reduction/ratio (RRR)?
• Which results from the table are significant? And Why?
• What is the meaning of a HR of 0.41 in the context of the this study?
• What is the significance of a 95% CI of 0.21-0.80?
• What is the significance of a p-value of 0.009?
• Despite the similarities in HR what do you think contributed to a vastly different 95%CI and p-value?
HR vs RRR

- HR reflects the ratio of incidence of an event in one group compared to another given a certain amount of time lapse since the beginning of the observation.
- RRR is the ratio of incident free subjects in one group compared to the comparator group at the end of a study.
Which results from the table are significant? And Why

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Culture & Sensitivity
Misnomers
Culture and Sensitivity

- Prior to initiation of Abx therapy, a C&S should be obtained
- Time table of information:
  - 24 Hours: morphology of the organism(s) including Gram stain results
  - 48 Hours: preliminary information with identification of organism and sensitivities
  - 5 days: finalized report (unless fungal or mycobacterium)
<table>
<thead>
<tr>
<th>Gram</th>
<th>Morphology</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Clusters</td>
<td>Staphylococcus spp (S. aureus)</td>
</tr>
<tr>
<td>Positive</td>
<td>Pairs and chains</td>
<td>Streptococcus or Enterococcus</td>
</tr>
<tr>
<td>Positive</td>
<td>Diplococci</td>
<td>S. pneumoniae</td>
</tr>
<tr>
<td>Negative</td>
<td>Coccibacilli</td>
<td>Haemophilus</td>
</tr>
<tr>
<td>Negative</td>
<td>Rods</td>
<td>Enterobacteriaceae Pseudomonas E. coli</td>
</tr>
<tr>
<td>Positive</td>
<td>Rods</td>
<td>Actinomyces or Nocardia spp</td>
</tr>
</tbody>
</table>
• “The abx with the lowest MIC is the best antibiotic”
  - Every abx has a given MIC range for S, I, and R and thus the MIC is specific to the given abx and organism
  - No comparison can be made between various abx based on MIC values as different concentrations of abx are tested to reflect human serum concentration
  - Sometimes the abx with the lowest MIC may be bacteriostatic vs bacteriocidal
  - Sometimes the abx with the lowest MIC may have limited penetration to the site of infection

*Remember think PKPD and not just PD!*
Culture and Sensitivity Interpretation

• “If the report states a bacteria is susceptible to a certain abx, you can use that abx”
  • Refer to misnomer #1
  • In the example of MRSA, often FQ, AG, and some CS may show susceptible but lack clinical utility
  • In the case of MRSA, clindamycin may show susceptible despite erythromycin induced clindamycin resistance
  • Automated C&S machines such as the VITEK which is used at SELF has a possible standard error of 1 fold change
    • Important to remember in serious infections and in patients who fail to respond to a certain abx which was shown as susceptible on the C&S report
Culture and Sensitivity Interpretation

• “Since a given bacteria is susceptible to a abx in a given class, it is susceptible to all abx in the class”
  • Despite being in the same class of abx, organism coverage may differ (FQ, CS, carbapenems, TC, macrolids)
  • PK parameters may differ from one abx to another within the class (FQ and TC)
Culture and Sensitivity Interpretation

- “A blood culture which grows out any bacteria is considered significant”
- “A urine culture which grows out any bacteria is significant”
- Treat the pt and not the number or the lab
- Estimations of BCx contamination is 30-90% (30% if >1 bottle positive, and 90% if 1 bottle only positive)
- Estimation of UCx contamination ranges from 20%-40% (based on sex and method)
- Asymptomatic bacteruria should not be treated per IDSA guidelines
“Since abx X is not on the C&S report, we can not use it”

If the only option is to use an abx not on the C&S report, the following is recommended:

- Ask microbiology department to perform a E-test if possible for the given abx with the given organism
  - Usually takes 24-48 hours for results
- Refer hospital antibiogram to determine the % of isolates previously sensitive to the given antibiotic
- Refer to other local antibiogram which would include the same patient population
Next Bugs and Drugs Noon Conference

- Discussion of treatment options for confirmed GP and GN resistant organisms
- De-escalation of therapy: when, how, and why
- Intravenous to oral conversion and when is it appropriate
- Monotherapy vs double/dual-coverage for resistant organisms
- Optimizing antibiotics based on pharmacokinetic properties (extended infusion, loading dose, continuous infusions...etc)
New PCSP ID Website

- At PCSP we are working on creating an infectious disease resource center webpage available to SRH Providers
- Please visit us at:

http://pharmacy.presby.edu/departments/pharmacy-practice/InfectiousDiseases

PLEASE SEND ANY SUGGESTIONS FOR THE WEBSITE TO EEGrace@Presby.Edu
Questions

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