Pharmacotherapy IV
Phar 6124
- Course sequence: ID, Tox, & Oncology
- Course Syllabus and Webpage
- Sanford Pocket Guides
- Infectious Diseases TA’s
  - Jeremy Schafer, Pharm D (Twin Cities)
  - Mike Schroeder (Duluth)
- Aminoglycoside Problem Set
- Web CT
  - Quizes
  - Aminoglycoside Pharmacokinetics Exam
- Final Exam

Antibiotic Pharmacodynamics
Bedside Applications
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Case
- Patient is a 19 year old male:
  - 94% TBSA thermal burn
  - 5 ft. 9 inches tall
  - 78 Kg (LBW 71 Kg)
- Vital Signs:
  - BP = 90/50 mmHg
  - HR - 170 per minute
  - T = 100.8 F
- Medication:
  - None & NKDA

PHYSICAL EXAM:
- 94% partial and full thickness burns of head and neck, upper and lower extremities
- Area spared were the genitalia, scalp, left upper chest
- HOSPITAL COURSE:
  - Transferred from North Dakota & admitted to Region’s Hospital Burn Unit
  - Intubated and hemodynamically stabilized
  - Escharotomies of upper and lower extremities

Cultures & Antibiotic Therapy

<table>
<thead>
<tr>
<th>Day</th>
<th>0ct8</th>
<th>11</th>
<th>14</th>
<th>17</th>
<th>20</th>
<th>23</th>
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<td>SC</td>
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<td>MRSA</td>
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Cultures

- Sputum:
  - S. aureus (MRSA) Oct. 11, 20, 24, & Nov. 12
  - E. cloace Oct. 11
  - Staph coag neg. Oct. 19, 22 and 24

- Blood:
  - S. aureus (MRSA) Oct. 11
  - Flavobacterium sp Oct. 11-26
**Flavobacterium spp**

- MIC Profile
  - Oct. 11-26
    - Gentamicin MIC = 4-8 mg/L
    - Piperacillin MIC = 8 mg/L

**October 25**

- Ceftazidime and Ciprofloxacin D/C
- Piperacillin 4Gm Q 6 H
- Gentamicin 160 mg Q 8 H
- Sandoglobulin
  - 35 GM IV 10/25
  - 20 GM 10/26
  - 20 GM 10/29

**October 27**

- Blood culture 10/25 &10/26 grew Flavobacterium spp resulted in consult
- D/C current antibiotics & start
  - Gentamicin 440 mg (~6 mg/kg) Q24H
  - Piperacillin Loading dose 3 Gm 2 hours after Gentamicin dose
  - Then Piperacillin continuous infusion at 500 mg/Hr (12 gm per day)
  - Levels
    - Piperacillin level once at steady state
    - Gentamicin pharmacokinetics per protocol

**Continuous Infusion of Piperacillin**

- Approach to continuous infusion
  - Total Daily Dose/ 24 hrs
  - Ko = Kd * Vd * Cp-ss
    - Assume T1/2 ~ 1 hr
    - Kd ~0.693/hr
    - Assume Vd ~ 0.2 ŁKg * 78 Kg = 15.6Ł
  - Cpss
    - Suggested Cp-SS = 4 to 10 X MIC
    - Flavobacterium MIC for piperacillin = 8 mg/L
    - Desired Cp-SS = 6 x 8 mg/L = 48 mg/L
    - Ko (mg/Hr) = 0.693 /hr * 15.6 Ł * 48 mg/L = 518.9 mg/Hr

**Continuous Infusion Piperacillin Results**

- Actual piperacillin Cp-ss = 22 mg/L at Ko = 500 mg/hr
  - Our estimate was Cp-ss = 48 mg/L
  - Actual Cp-ss ~3 X MIC not 6 X MIC
- CI = KoCpss
- CI = 500 mg/Hr / 22 mg/L = 22.7 L/hr
  - Our estimate for clearance = 10.8 L/hr
  - Actual clearance ~ 2 X greater than estimate
- Ko = CI x Cpss
- Ko = 22.7 L/hr x 48 mg/L = 1089.6 mg/hr
  - > 24 Gm / Day Piperacillin or ~ 2X current dose

**SDD Pharmacokinetic Studies**

<table>
<thead>
<tr>
<th>Day &amp; Date</th>
<th>Cp-x (mg/L)</th>
<th>T1/2 (hr)</th>
<th>Vd (ŁKg)</th>
<th>Cp-X: MIC</th>
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</thead>
<tbody>
<tr>
<td>1 Oct. 27</td>
<td>17.2</td>
<td>1.9</td>
<td>0.28</td>
<td>4.3</td>
</tr>
<tr>
<td>2 Oct. 28</td>
<td>14.6</td>
<td>1.7</td>
<td>0.32</td>
<td>3.7</td>
</tr>
<tr>
<td>4 Oct. 30</td>
<td>15.7</td>
<td>1.8</td>
<td>0.32</td>
<td>3.9</td>
</tr>
<tr>
<td>5 Oct. 31</td>
<td>14.1</td>
<td>0.9</td>
<td>0.31</td>
<td>3.5</td>
</tr>
<tr>
<td>6 Nov. 1</td>
<td>20.6</td>
<td>1.1</td>
<td>0.22</td>
<td>5.2</td>
</tr>
<tr>
<td>8 Nov. 3</td>
<td>14.5</td>
<td>1.6</td>
<td>0.33</td>
<td>3.6</td>
</tr>
<tr>
<td>30 Nov. 27</td>
<td>20.1</td>
<td>1.5</td>
<td>0.25</td>
<td>5.0</td>
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</table>
Case Summary

- Flavobacterium spp cleared from blood in 24 hr
  - Result of our intervention
    - Was the outcome because of the continuous infusion of piperacillin, the SDD approach with gentamicin, or both?
    - Did the gentamicin strategy contribute at all?
  - Result of combination immunoglobulin &/or previous therapy
- Ultimate outcome: patient survived

Therapeutic Goals

- **Select most potent class agent**
  - Optimize pharmacodynamic outcome parameter by selecting class agent with lowest MIC
    - Example *P. aeruginosa*: Piperacillin, Cefepime, Imipenem/Meropenem, Tobramycin, & Ciprofloxacin/Lевофлоксацин
  - Use hospital and ward specific antibiogram data

- **Strategy for combination therapy**
  - Use antibiotics of different chemical class
  - Use antibiotics with different MOA
  - Use antibiotics with different PD profile
    - Concentration dependent vs independent killers

**Therapeutic Goals**

ATS HAP/VAP/HCAP Guidelines 2005

- **Antibiotic combinations for *P. aeruginosa***
  - Unclear Two vs One Antibiotic But:
    - Infection associated with high morbidity/mortality
    - Increase odds of providing at least 1 effective agent
    - Possible synergy or additive effect
    - Suppress emergence of resistant mutants
    - Suppress release of endotoxin
    - Suppress glycocalyx production

Therapeutic Goals

- **Sequence the antibiotic combination**
  - Use concentration dependent agent first
    - Example: Aminoglycoside, fluoroquinolone, ect.
    - Quickly & significantly reduce initial bacterial burden
      - Reduce bacterial burden by > 3 logs of CFU/ml in compromised host
  - Follow with concentration independent agent
    - Example: Beta-lactam
    - Loading dose followed by continuous infusion
    - Suppress emergence of resistance &/or regrowth

Therapeutic Goals

- **Optimize the value of the pharmacodynamic (PD) outcome parameter for each agent**
  - Most potent class agent for better MIC profile
  - Dose will affect AUC & Cpmax but MIC can double or half PD outcome parameter value
  - Example
    - *P. aeruginosa* vs Tobramycin or Gentamicin
      - MIC
        - Gentamicin MIC = 1mg/L vs Tobramycin MIC 0.5mg/L
      - Peak Concentration
        - Gentamicin Cmax 8mg/L vs Tobramycin Cmax 8 mg/L
      - Peak/MIC Ratio
        - Gentamicin = 8 vs Tobramycin = 16
      - Same dose, same peak concentration but peak/MIC ratio doubled

How Should Aminoglycoside be Administered?

Hartford Program: Single Daily Dosing (7 mg/Kg/day) of Aminoglycosides

- Based on worst case scenario *P. aeruginosa* gentamicin MIC\_{50}^\text{g} = 2 mg/ L
- Previous studies demonstrated maximum clinical response when Cpx ~ 10X MIC
- To produce Cpx = 20 mg/ L requires dose of 7 mg/Kg/day (based on 1 compartment model)
- Had the investigators used the same rationale but: Substituted tobramycin for gentamicin the recommended dose would be ≤ 3.5 vs 7 mg/Kg/day
Case Report

- 53 year old male involved in MVA with multiple head & abdominal injuries. Admitted 12 days ago to SICU placed on respirator 8 days ago
- Short exposure to several different antibiotics including vancomycin, P/T, imipenem, gentamicin, & ciprofloxacin in different combinations
- Patient spikes temperature to 103.5 F
- WBC’s increase to 21,000/mm3 & CXR demonstrates new infiltrate
- Following culture results are returned from BAL specimen obtained ~24 hours ago

Antibiotic Resistant

*P. aeruginosa*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>P. aeruginosa #1</th>
<th>P. aeruginosa #2</th>
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<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;4</td>
<td>&gt;4 (≥4)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;32</td>
<td>32 (≥32)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>16</td>
<td>8 (≥16)</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt;16</td>
<td>&gt;16 (≥16)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;16</td>
<td>&gt;16 (≥16)</td>
</tr>
<tr>
<td>Colistin</td>
<td>0.125</td>
<td>0.125</td>
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</table>


Colistin Sensitivity Testing

- Agar diffusion methods not reliable as drug does not diffuse through the media well
- Big issue of whether colistin sulfate or methanesulfonate is used in testing because of potency differences

Role of Pharmacodynamics in Developing Antibiotic Dosing Strategies

Can we reinvent Colistin?

By changing the nature &/or magnitude of colistin exposure can we:
- Maximize antibiotic efficacy?
- Minimize antibiotic induced toxicity?

Colistin

- Colistin identified in 1950 (*B. colistinus*)
  - Polycationic peptide ring of 8-10 amino acids with substituted 2, 4-diamino-butryic (DAB) acid residues
  - Fatty acid (FA) side chain attached to peptide ring
    - Colistin A (Polymyxin E1) 6-methyl-octanoic acid
    - Colistin B (Polymyxin E2) 6-methyl-heptanoic acid
  - Combination of DAB and fatty acid side chain give colistin amphipathic properties
  - MW 1200
- First clinical use 1959
- Colistin methanesulfonate introduced in 1961
Polymyxins

**Mechanism of Action**

- **Physiochemical action**
  - Interacts with LPS and phospholipids of outer membrane & inhibits the release of endotoxin
  - Cause electrostatic interference of outer membrane
  - DAB displace divalent cation (Ca++ and Mg++) bridges that stabilize LPS
  - Overall effect causes leakage, a dysfunctional outer membrane, and cell death

**Simulated Colistin Parameters**

<table>
<thead>
<tr>
<th>Cmax (mg/L)</th>
<th>( T_{1/2} ) (Hrs)</th>
<th>AUC</th>
<th>AUC/MIC</th>
<th>Cmax/MIC</th>
<th>T&gt;MIC</th>
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<tbody>
<tr>
<td>6 mg/L IM use</td>
<td>3 hours</td>
<td>26 mg hr/L</td>
<td>208</td>
<td>48</td>
<td>70%</td>
</tr>
<tr>
<td>18 mg/L IV use</td>
<td>3 hours</td>
<td>78 mg hr/L</td>
<td>624</td>
<td>144</td>
<td>90%</td>
</tr>
</tbody>
</table>

**Colistin vs P. aeruginosa**

**Graphs**

- Colistin 8 mg/L single dose
- Colistin 18 mg/L single dose


Colistin QD Dosing
David Smith 2002

- At Methodist Hospital of Indiana multi-drug resistant P. aeruginosa and A. calcoaceticus baumannii complex isolates remain rare. However, isolates resistant to conventional agents but susceptible to colistin are encountered……..

- Colistin is dosed as: 5 mg/kg q24hr in patients with creatinine clearance > 60mLmin.
  q36hr in patients with creatinine clearance 40 - 59 mL/min.
  q48hr in patients with creatinine clearance 20 - 39 mL/min.
  q72 - 96 hr in patients with creatinine clearance < 20 mL/min.

Clinical Case
- 12 yr 50Kg male suffered 68% BSA burn
  - Hospitalized for 5 months multiple courses of antibiotic including aminoglycosides
    - Scr = 0.9 mg/dl but no lean body mass
    - Previous nephrotoxic episodes with tobramycin
    - Mismatch between age & Scr with tobramycin T1/2
  - Positive blood & sputum cultures for P. aeruginosa
    - Amikacin 16mg/L, gentamicin 8mg/L, tobramycin 8mg/L, imipenem >16mg/L, P/T >128/4mg/L, & Ceftazidime >32mg/L
    - Meropenem R, Ceftazidime >128mg/L(Estrip), & colistin 2mg/L

Bedside Application Summary
- General & individualized pharmacodynamic applications
  - Target attainment may prevent or delay the development of antibiotic resistance
  - Focused application may rescue select patients at risk of failure
    - Patient’s with resistant pathogens
    - Patient’s who are hyperdynamic

Clinical Case
- Started on colistin 5mg/Kg loading dose then 2.5 mg/Kg Q24H & ceftazidime loading dose then 250 mg/Hr continuous infusion
  - Attempted informed consent from parents
  - Colistin pre < 5mg/L, 25 min post 23 mg/L, & 8 hour post < 5 mg/L
  - Ceftazidime Cpp = 32 mg/L
  - Patient completed ~2wks therapy, although positive blood culture for VRE no further P. aeruginosa isolated from blood
  - Patient survived