The New Adventures of Old Antibiotics

Scott Bergman, Pharm.D., BCPS (AQ ID)
Southern Illinois University Edwardsville
School of Pharmacy & St. John’s Hospital PGY2
Infectious Diseases Residency Director
Springfield, IL

Objectives for Pharmacists

• Discuss the evidence for the use of older antibiotics in treating infections caused by multidrug resistant pathogens
• Identify possible toxicities of the older antibiotics and suggest potential management or treatment for those toxicities

Outline

• Case
• Polymyxins
• Fosfomycin
• Summary
• Questions

Case

• BP is 37 yo male patient admitted to the burn unit following an accident that involved pouring lighter fluid on a campfire.
• He has been diagnosed with third degree burns to 70% of his body surface area including respiratory tract inhalation injury
• BP is ventilated and has a central venous catheter as well as a foley urinary catheter

Disclosures

• I have no potential conflicts of interest for this presentation

Case

• He is being treated with ceftriaxone for early-onset pneumonia with H. influenzae
• After 6 days of treatment, he is not improving and cannot be weaned from the vent.
• Repeat bronch samples show Gram negative coccobacilli and blood cultures grow Acinetobacter baumannii
• Susceptibilities are performed and show...
**Acinetobacter baumannii case**

- Amikacin = I
- Ampicillin/sulbact. = R
- Ciprofloxacin = R
- Imipenem = R
- Gentamicin = R
- Tobramycin = R
- Trimethoprim/sulfa = R

- An infectious diseases consult is placed and they recommend testing for polymyxin B, tigecycline, and doripenem

**Polymyxins**

- Polymyxin B discovered in 1947
  - Bacillus polymyx
- Colistin (Polymyxin E) 1949-50
  - B. polymyx subspecies colistinus
- High incidence of nephro- and neurotoxicity
- Replaced in the 1980’s by the “safe”, new aminoglycosides for gram-negative infections

**Polymyxin toxicities**

- Dose dependent, usually reversible
- Neurotoxicity (7-27% in early studies)
  - Parasthetias, vertigo and/or ataxia
  - More frequent in cystic fibrosis?
- Nephrotoxicity (15-36% before, now 8%?)
  - Different formulations, doses and concurrent therapies studied
- Hypersensitivity (2%)

**Polymyxins**

- Polymyxin B
- Colistin (Polymyxin E)

**Mechanism of action**

- Acts as a detergent on the bacterial cell membrane
- Displaces Ca**+, Mg**
- Attaches to LPS
- Destabilizes cell
- Increases perm.
- Causes efflux of cell contents
- Leads to death of the bacteria

**Polymyxins**

- Concentration-dependent, bactericidal
- Modest post-antibiotic effect
- Active against most multidrug resistant (MDR) aerobic gram-negative organisms
  - Pseudomonas aeruginosa
  - Acinetobacter baumannii
  - E. coli, Klebsiella and Enterobacter sp.
  - Stenotrophomonas maltophilia

Arnold, TM. Am J Health-Syst Pharm. 2007
Polymyxins

- Inherently NOT effective against:
  - Proteus, Providencia, and Serratia sp.
  - Neisseria meningitidis and N. gonorrhoeae
  - Burkholderia cepacia
  - Anaerobes (Bacteroides fragilis)
  - Gram positives (Staph, Strep, & Enterococcus)
- Acquired resistance is rare, but possible
  - Susceptibility performed manually by Etest

Arnold, TM. Am J Health-Syst Pharm. 2007

Polymyxin B

- IV Dose: 15-25,000 units/kg/day divided q12h
  (or by continuous infusion, not advisable)
- Intrathecal: 50,000 units once daily x 3-4 d,
  then every other day for 2 weeks after CSF (-)
- Topically: Polysporin ointment with bacitracin
  or Neosporin (triple antibiotic) with neomycin
- Ophthalmic suspension also available
  - With Trimethoprim in PolyTrim

Colistin

- Colistimethate sodium (Coly-Mycin M) IV/IM
  - Inactive prodrug (CMS) converted to colistin
    - 150 mg vial “colistin base” is 360 mg
      colistimethate or 4,500,000 units (30,000 IU/mg)
- Internationally: Colistin methanesulfate
  (Colomycin) dosed in units
- Colistin sulfate tablets (and syrup)
  - Not absorbed orally, not interchangeable with IV
  - Used for bowel decontamination

Maviglia, R. Curr Drug Targets 2009
Arnold, TM. Am J Health-Syst Pharm. 2007

Colistin elimination

- Not removed by hemodialysis
- Not particular good for UTIs

Colistimethate dosing

- Half-life = 1.5 hours IV
- Recommended dose: 2.5-5 mg/kg colistin base per day, divided into 2-4 doses
  - In obesity, ideal body weight is preferred
  - 75-100 mg q 8h, safer than 150mg q12h?
- Distribution to organs and tissue is high
- Poor penetration into the lungs and CSF
  - 15-25%

Colistimethate administration

- Intrathecal or intraventricular route can be used for MDR meningitis
  - 10 mg/day with systemic therapy
- Inhalation is recommended for treatment of MDR pneumonias
  - 50-75 mg in NS (3-4 mL) via nebulizer 2-3 times/d
  - Black box warning: bronchospasm

ATS/IDSA Guidelines for HAP, VAP and HCAP. Am J Respir Crit Care Med. 2005
Inhaled colistin efficacy

• Several studies have compared IV plus inhaled colistin to IV therapy alone for MDR VAP
• All are small, retrospective, case-controlled
• One has shown a clinical benefit
• Cure: 79.5% vs. 60.5% (62/78 vs. 26/43 pts)
  – OR 2.53, 95% CI 1.11-5.76
  – No difference in mortality (39.7% vs. 44.5%)
  – Lower IV colistin dose was predictor of success


Combination therapy

• Colistin plus an antipseudomonal antibiotic
  – Piperacillin, ceftazidime, imipenem, aztreonam, or ciprofloxacin among others
  – More effective than colistin alone against P. aeruginosa in cystic fibrosis patients
• Colistin and rifampin +/- amikacin
  – Synergy against carbapenemase-producing Acinetobacter & Klebsiella pneumoniae
  – May allow lower doses thus reducing toxicity

Falagas, ME. Clin Infect Dis. 2005

Managing toxicities

• Supportive care
• Administer normal saline
• Use a lower IV dose
  – Consider combination therapy with inhaled colistin or systemic rifampin (amikacin?)
• Shorten course
• Remove prosthetic devices

Comparative toxicity

<table>
<thead>
<tr>
<th></th>
<th>Colistin, n=7</th>
<th>Polymyxin B, n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Scr, Mean (±SD)</td>
<td>0.87 mg/dL (0.18)</td>
<td>0.86 mg/dL (0.20)</td>
</tr>
<tr>
<td>Dose, Mean (±SD)</td>
<td>3.46 mg/kg/day (1.38)</td>
<td>15,952 units/kg/day (4450)</td>
</tr>
<tr>
<td>Duration, Median (range)</td>
<td>14 days (8-33 days)</td>
<td>13 days (3-26 days)</td>
</tr>
<tr>
<td>Nephrotoxicity, n (%)</td>
<td>5/7 (71%)</td>
<td>4/18 (22%)</td>
</tr>
<tr>
<td>OR = 12.5 (CI 95% 1.6-97.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bergman SJ. ICAAC. 2010

Fosfomycin

• Discovered in 1969, approved in 1996
• Structurally similar to a precursor responsible for the synthesis of peptidoglycan
• Blocks formation of bacterial cell wall instead of preventing cross linking as β-lactams do

Fosfomycin \[\text{Phosphoenolpyruvate}\]

Stein GE. Clin Ther. 1999

Fosfomycin

• Oral granule sachet in the U.S. (Monural)
  – Also available IV in Europe
• High urinary concentrations, but low systemic levels (not for bloodstream infection)
  – Half-life is extended in renal insufficiency
  – Similar to nitrofurantoin, but toxicity not apparent
    * Diarrhea (2.4%), vaginitis (1.8%), nausea (0.8%)

Stein GE. Clin Ther. 1999
Fosfomycin spectrum

- Active against most Enterobacteriaceae
  - *E. coli*, *Klebsiella*, *Enterobacter*, *Proteus*, *Serratia* and *Morganella* species among others
- Also works against *Staphylococcus saprophyticus* and *Enterococcus* sp.
  - Including VRE

Falagas, ME. *Lancet Infect Dis*. 2010

Fosfomycin dosing

- Uncomplicated urinary tract infections (UTIs): Single oral dose of 3 g in 3-4 oz water
- Complicated UTIs (off-label), Ex: Males or hospital-acquired MDR pathogens
  - 3 g po every 2-3 days for 3 doses
- Has been studied as an option in pregnancy

Falagas, ME. *Lancet Infect Dis*. 2010

Fosfomycin efficacy

- Randomized trials of a single dose for uncomplicated UTIs resulted in similar outcomes compared to:
  - 7 days of treatment with norfloxacin (1991) or nitrofurantoin (1999)


Fosfomycin efficacy

- Retains *in vitro* activity even against those MDR Gram-negative organisms that produce extended spectrum beta-lactamases (ESBLs) and carbapenemases
- Greater than 90% susceptibility for:
  - ESBLs: SHV, TEM, ampC
  - Carbapenemases: KPC, NDM

Falagas, ME. *Lancet Infect Dis*. 2010

Fosfomycin efficacy

- Two trials have compared oral fosfomycin for lower UTIs with ESBL-producing *E. coli*
  - Single dose vs. amoxicillin-clavulanate 5-7 days
    - Cure: 93% vs. 84% overall or 93% if susceptible
    - 26/28 and 31/37 (or 26/28) patients
  - Three doses given once every other night
    - For ciprofloxacin and TMP/SMX resistant isolates
    - Cure: 49/52 (94.2%), microbiological success 7-9 d later: 41/52 (78.8%), no relapses 0/28


Summary

- Polymyxins & fosfomycin are old antibiotics that can be used to treat new MDR Gram-negative infections
- Lowering the IV colistin dose and using inhaled or other adjunctive therapy may help balance safety and efficacy
- Oral fosfomycin can only be used to treat urinary tract infections, but known toxicity is limited
Case revisited

- Antimicrobial susceptibility testing comes back susceptible to polymyxin B, intermediate to tigecycline and resistant to doripenem
- Infectious diseases would like to start colistin, but wants you to monitor the patient.

Question 1

Which two side effects must be monitored for closely when using polymyxin antibiotics?
A. Nephrotoxicity and ototoxicity
B. Neurotoxicity and hepatotoxicity
C. Nausea and vomiting
D. Nephrotoxicity and neurotoxicity
E. Diarrhea and hepatotoxicity

Question 2

Which one of these bacteria are polymyxin B and colistin not effective against?
A. Acinetobacter baumannii
B. Pseudomonas aeruginosa
C. Enterococcus faecium
D. Klebsiella pneumoniae
E. Escherichia coli

Question 3

Which of these is true of oral fosfomycin?
A. It is only effective for infections of the urinary tract
B. Its use is limited by toxicity, primarily nausea
C. It can cause birth defects
D. It works by inhibiting the protein synthesis
E. The usual duration of therapy is 2 weeks

Honorable Mention

- Fusidic Acid*
- Chloramphenicol
- Minocycline (Tigecycline)
- Trimethoprim (Iclaprim)
- Aminoglycosides (Inhaled amikacin-liposomal)
- Inhaled Aztreonam (Kayston®)

*Moellering RC. Clin Infect Dis. 2011; 52 (suppl 7)

The New Adventures of Old Antibiotics

Scott Bergman, Pharm.D., BCPS
ScBergm@siue.edu