Novel Strategies and Agents for Treatment of MDR Gram Negative Infections

Daniel J.G. Thirion BPharm, MSc, PharmD, FCSHP
Full Clinical Professor, Faculté de pharmacie, Université de Montréal
Pharmacist, Royal Victoria Hospital/MUHC
Disclosures

- Education grants, advisory boards, or speaker bureaus for the following organizations:
  - BioMérieux
  - Merck Canada
  - Profession Santé
  - Toc Toc Communications
Case Introduction

- KK, male, 66 yo, admitted in February 2019 for recurrent infected renal calculi. Also complicated by candida L1-L2 spondylodiscitis (caspo, followed by oral voriconazole). Known for previous prolonged hospitalisations with multiple complications.

- March 23rd, febrile episode most likely urinary source
- Initially treated with piperacillin/tazobactam
- Urine cultures: *E. coli*, 4 different strains. One strain resistant to all antibiotics (OXA 48)
- Treatment changed to meropenem + colistin
- Now complains of dizziness
Objectives

- Novel strategies
- Extended/Prolonged/Continuous infusion
- Combination of agents
- Phage treatments
- Agents
  - Ceftolazone/tazobactam
  - Fosfomycine
  - Tigecycline
  - Ceftazidime/avibactam, Aztreonam/avibactam
  - Plazomicin
Dosing matters: extended infusions of Pip/tazo for *P. aeruginosa*

![Graph showing probability of target attainment vs MIC (mcg/mL)]

- **3.375 Q6h**
- **3.375 Q4h**
- **4h infusion of 3.375 Q8h**

MIC (mcg/mL) range: 0.25 to 32

Probability of Target Attainment range: 0 to 1

Extended Infusion of Pip/tazo in Susceptible *Pseudomonas aeruginosa* infections

- 194 patients -102 with extended infusions (EI)
- No differences in baseline pt characteristics
- Patients with APACHE II ≥17
- 14 day mortality significantly less in EI arm (P=.04)

Combination therapy: Mortality Rates of Patients with Carbapenemase Producing *Klebsiella pneumoniae*

- A: Inappropriate therapy (no drug active *in vitro*)
- B: Monotherapy (one drug active *in vitro*)
- C: Combination therapy (2 or more drugs active *in vitro*)
  - C1: Combination therapy with 2 or more drugs active *in vitro*, including one being a carbapenem (MIC <8mg/L)
  - C2: Combination therapy with 2 or more active drugs *in vitro*, not including a carbapenem

N = 2972 (meta-analysis)

Timeline of major events in the history of research on phages, phage therapy, and antibiotics.

1896: Hanke Antiseptic action of river water against Vibrio cholerae.
1915: Twort “Bacteriolytic agents of enzymatic nature.”
1919: Birth of phage therapy. Dysentery cases cured using phage plaques.
1929: Fleming First mention of penicillin.
1940: Ruska First EM image of a phage.
1940s-1970s: Golden Age of Antimicrobials: 40 antibacterial compounds discovered and introduced.
1960: Soothill Merrill et al. Resurgence of phage therapy studies with animal models.
2000: Number of new antibiotics decreases. Start of dry pipeline phenomenon.
2015: Wright et al. First phase III controlled clinical trial of phage therapy.
1920s: Expansion of phage therapy trials: cholera, dysentery, bubonic plague, conjunctivitis, skin infections.
1933-1934: d'Herelle “Bacteria are susceptible to infection and are hosts to ultramicroscopic agents, named Bacteriophages.”
1977: Sanger First phage genome sequenced.

# Phage Therapy and Antimicrobials

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Similarities</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity: does not kill the microbiota</td>
<td>Administration requires a neutralized-pH environment</td>
<td>Specificity: causative bacterium must be identified beforehand, narrow spectrum of action</td>
</tr>
<tr>
<td>Self-limitation: once the bacterial host is killed, it ceases to function</td>
<td>Therapeutic success depends on variables such as time of treatment initiation</td>
<td>Induction of phage-neutralizing antibody production (clinical relevance to be determined)</td>
</tr>
<tr>
<td>Available for patients with antibiotic allergies</td>
<td>Activity is influenced by the immune system of the patient</td>
<td>Significantly smaller body of evidence and correctly designed clinical trials supporting its effectiveness</td>
</tr>
<tr>
<td>Safety: no effects on mammalian cells</td>
<td>Versatility in routes of administration</td>
<td>Lack of a specific regulatory framework, and legal issues regarding intellectual property</td>
</tr>
<tr>
<td>Exponential reproduction allows for lower doses</td>
<td>Occurrence of bacterial resistance to the therapeutic agent</td>
<td></td>
</tr>
<tr>
<td>Evolution: if resistance arises, phages mutate alongside bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiofilm activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple and inexpensive to produce</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ubiquity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1 Intrinsic and acquired beta-lactamases in *Enterobacteriaceae*. 
# β-lactamase inhibitors

<table>
<thead>
<tr>
<th>Clavulanate</th>
<th>Tazobactam</th>
<th>Avibactam</th>
<th>Relebactam</th>
<th>Cilastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irreversible binding to Class A β-lactamases</td>
<td>Irreversible binding to Class A β-lactamases</td>
<td><strong>Covalent reversible binding</strong> (recycling/turover leading to inactivation of other β-lactamases)</td>
<td><strong>Covalent binding</strong> to β-lactamases</td>
<td>Inhibition of renal dehydropeptidase (inhibition of imipenem metabolism in the kidney)</td>
</tr>
<tr>
<td>Activity:</td>
<td>Activity:</td>
<td>Active against class A (including ESBLs and KPCs)</td>
<td>Active against class A (including ESBLs and KPCs)</td>
<td>Active against class A (including ESBLs and KPCs)</td>
</tr>
<tr>
<td>Class A (including some ESBLs, not KPCs)</td>
<td>Class A (including ESBLs, not KPCs)</td>
<td>Active against class C (AmpC)</td>
<td>Active against class C (AmpC)</td>
<td>Active against class A (including ESBLs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active against class D</td>
<td></td>
<td>Active against class C (AmpC)</td>
</tr>
</tbody>
</table>
Target beta-lactamase: tazobactam vs avibactam

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Class</th>
<th>Substrates</th>
<th>Tazobactam</th>
<th>Avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEM-1, TEM-2, SHV-1</td>
<td>A</td>
<td>Penicillins, early cephalosporins</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>TEM-3, SHV-2 CTX-M-14</td>
<td>A</td>
<td>Extended-spectrum cephalosporins, monobactams</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>KPC-2, KPC-3</td>
<td>A</td>
<td>Broad spectrum including carbapenems</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>IMP-1, NDM-1, VIM-1</td>
<td>B</td>
<td>Broad spectrum including carbapenems, but not monobactams</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><em>Escherichia coli</em> AmpC</td>
<td>C</td>
<td>Cephalosporins</td>
<td>High concentrations</td>
<td>Yes</td>
</tr>
<tr>
<td>OXA-48</td>
<td>D</td>
<td>Carbapenems</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviation: KPC, Klebsiella pneumoniae carbapenemase

Treatment algorithm of GNB – BCAS 2018
## New Antibiotics in Development

### Table 2

Summary of Antimicrobial Agents in Clinical Development

<table>
<thead>
<tr>
<th>Drug Developer(s)</th>
<th>Mechanism of Action</th>
<th>Targeted Indication/Population</th>
<th>Route and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam/avibactam Pfizer</td>
<td>Mono-bactam antibiotic plus beta-lactamase inhibitor</td>
<td>Serious gram-negative infections, including cIAI, cUTI, HAP/VAP, and patients with penicillin allergies</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose ranges under study: 4,250–6,500 mg ATM/1,162–2,167 mg AVI on day 1, followed by daily dosing of 3,000–6,000 mg ATM/820–2,000 mg AVI</td>
<td></td>
</tr>
<tr>
<td>Cefiderocol Shionogi and Co. Ltd.</td>
<td>Cephalosporin antibiotic</td>
<td>MDR gram-negative infections, including CRE, <em>P. aeruginosa</em>, and <em>A. baumannii</em></td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 g every 8 hours</td>
<td></td>
</tr>
<tr>
<td>Eravacycline Tetraphase Pharmaceuticals</td>
<td>Tetracycline antibiotic</td>
<td>Hospital-acquired infections caused by MDR gram-negative bacteria, including cUTI and cIAI</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1–1.5 mg/kg every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Finafloxacn MerLion Pharmaceuticals</td>
<td>Fluoroquinolone antibiotic</td>
<td>Treatment of cUTIs and possibly lower respiratory, skin, and soft-tissue infections</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Plazomicin Achaogen</td>
<td>Aminoglycoside antibiotic</td>
<td>MDR gram-negative bacteria, including ESBL and CRE organisms</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg/kg once daily</td>
<td></td>
</tr>
<tr>
<td>Imipenem/cilastin/ relebactam Merck</td>
<td>Beta-lactam antibiotic plus beta-lactamase inhibitor</td>
<td>Hospital-acquired infections caused by MDR gram-negative bacteria, including cUTI, cIAI, and pneumonia</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 mg relebactam/500 mg imipenem/cilastatin every 6 hours</td>
<td></td>
</tr>
</tbody>
</table>
# Pharmacology

**ceftolozane/tazobactam**

<table>
<thead>
<tr>
<th>Ceftolozane</th>
<th>Tazobactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>New cephalosporin</td>
<td>Beta-lactamase inhibitor already known</td>
</tr>
<tr>
<td>Bactericidal</td>
<td></td>
</tr>
<tr>
<td>Inhibition of PBP (destruction of cell wall that results in cell death)</td>
<td>Inhibits class A (ESBL) and some class C (AmpC)</td>
</tr>
<tr>
<td>Higher affinity than ceftazidime or imipenem for certain PBP (1b, 1c, 3)</td>
<td>Irreversible covalent binding</td>
</tr>
<tr>
<td>Retains activity for common resistance mechanisms in <em>P. aeruginosa</em> (OprD loss, MexXY and MexAB efflux pump)</td>
<td>Prevents hydrolysis of ceftolozane</td>
</tr>
</tbody>
</table>

[Figure 1: Chemical Structure of Ceftolozane/Tazobactam](#)
Ceftolozane/tazobactam Clinical Trials

- **ASPECT study** (randomized multinational double blind phase 3 trial)
  - cIAI: Non-inferior to meropenem for treatment of complicated intra-abdominal infections (in combination with metronidazole)
  - cUTI: Non-inferior to levofloxacin for treatment of complicated urinary tract infections
- Ceftolozane/tazobactam commercialized in Canada since 2017

References:
Ceftolozane/tazobactam
Recommendations BCAS 2018

Recommendations

- Use ceftolozane/tazobactam to treat susceptible *P. aeruginosa* infections resistant to ceftazidime.
  Grading: Conditional recommendation for
- Conduct clinical trials in *P. aeruginosa* infections in cystic fibrosis.
  Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials
- Use ceftolozane/tazobactam as an alternative to carbapenems to treat urinary or intra-abdominal infection involving ESBL-producing *E. coli*. Caution may be needed when treating infection due to ESBL-producing *Klebsiella* spp. owing to a higher resistance rate.
  Grading: Conditional recommendation for
- Do not use for infections due to AmpC- or carbapenemase-producing *Enterobacteriaceae* or MBL/ESBL-producing *P. aeruginosa*.
  Grading: Strong recommendation against use

Hawkey PM. et al. J Antimicrob Chemother 2018; 73 Suppl 3: iii2-iii78
# Ceftazidime/avibactam (pharmacology)

<table>
<thead>
<tr>
<th>Ceftazidime</th>
<th>Avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known cephalosporin</td>
<td>Novel β-lactamases inhibitor (no beta-lactam</td>
</tr>
<tr>
<td>Bactericidal</td>
<td>ring)</td>
</tr>
<tr>
<td>Inhibition of PBP (destruction of</td>
<td><strong>Covalent reversible binding</strong> to β-lactamases</td>
</tr>
<tr>
<td>cell wall that results in cell</td>
<td>(recycling/turnover leading to inactivation of</td>
</tr>
<tr>
<td>death)</td>
<td>other β-lactamases)</td>
</tr>
<tr>
<td></td>
<td>Class A (ESBL and KPC), Class C (AmpC) and</td>
</tr>
<tr>
<td></td>
<td>Class D (OXA) β-lactamases inhibition</td>
</tr>
</tbody>
</table>
Ceftazidime/avibactam
Recommendations BCAS 2018

Recommendations

- Could use ceftazidime/avibactam as an alternative to carbapenems for infection with ESBL- and AmpC-producing Enterobacteriaceae but alternatives may be cheaper. Grading: Conditional recommendation for
- Evaluate further ceftazidime/avibactam use alone or in combination when non-MLB carbapenemase-producing organisms cause infection. KPC-3-producing Klebsiella spp. are vulnerable to mutations in the blaKPC-3 gene causing resistance. Grading: Recommendation for research and possibly conditional recommendation for use restricted to trials
- Do not use for treating infection with anaerobes or bacteria producing MBLs: these are resistant. Grading: Strong recommendation against

Hawkey PM. et al. J Antimicrob Chemother 2018; 73 Suppl 3: iii2-iii78
**Aztreonam/avibactam (pharmacology)**

<table>
<thead>
<tr>
<th></th>
<th>Aztreonam</th>
<th>Avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monobactam</td>
<td>Novel β-lactamase inhibitor (no β-lactam ring)</td>
<td>Covalent reversible binding (recycling/turnover leading to inactivation of other β-lactamases)</td>
</tr>
<tr>
<td>Inhibition of PBP (destruction of cell wall that results in cell death)</td>
<td>Does not contain a β-lactam ring</td>
<td></td>
</tr>
<tr>
<td>Monobactam structure that is not hydrolyzed by Class B beta-lactamases (metallo enzymes)*</td>
<td>Active against class A (including ESBLs and KPC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active against class C (AmpC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active against class D</td>
</tr>
</tbody>
</table>

*Metallo-enzymes: hyrdolyse all beta-lactams but not the monobactams such as aztreonam*
Recommandations BCAS 2018

Recommendations

- Do not use aztreonam alone empirically if MDR GNB or Gram-positive or anaerobic pathogens are suspected. Grading: Strong recommendation against use.
- Do not use aztreonam for CTX-M ESBL- or AmpC-producing bacteria even if these appear susceptible *in vitro*. Grading: Strong recommendation against use.
- Use aztreonam for MBL- or OXA-48-producing strains if it is certain that they do not produce ESBLs or AmpC. Grading: Conditional recommendation for.
- Research usefulness of aztreonam in combination with avibactam for bacteria producing MBLs with ESBL/AmpC enzymes and for those with other carbapenemases. Grading: Recommendation for research.

Plazomicin

- Next generation aminoglycoside
- Activity against aminoglycoside modifying organisms
- Phase III trial
  - Noninferior to meropenem for cUTIs (n=288)
- Effective in treatment of carbapenem resistant *Enterobacteriacea* and less mortality (23%, 4/17) compared to colistin (50% n=10/20)
- Side effects as expected with aminoglycosides (nephro-, ototoxicity, neuromuscular blockade, fetal harm)

Fosfomycin, Fosfomycin tromethamine

- Inhibits phosphoenolpyruvate transferase: interferes with peptidoglycan synthesis
- Bioavailability 40%, extensive tissue distribution,
- Spectrum of activity: *S. aureus* (MRSA), *S. pyogenes*, *S. pneumonia*, *Enterococcus* (VRE), *Citrobacter* sp, *E. coli*, *Klebsiella oxytoca*, *Proteus mirabilis*
- Acquired resistance may be a problem: *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Serratia marcescens*
- Used in combination (beta-lactams, carbapenems, aminoglycosides)
- Good safety profile (hypokalemia, GI), few drug interactions
Tigecycline

- Glycylcycline with broad spectrum of activity
- **Gram-positive bacteria:** *S. aureus* (MRSA), *Staphylococcus epidermidis* (MRSE), *Enterococcus faecalis*, *Enterococcus faecium* (VRE), *Streptococcus anginosus* group, *Streptococcus pyogenes*, and *S. pneumoniae*.
- **Gram-negative bacteria:** *Citobacter freundii*, *Enterobacter cloacae*, *E. aerogenes*, *E. coli*, *Klebsiella oxytoca*, *K. pneumoniae*, and *Stenotrophomonas maltophilia*, *Neisseria gonorrhoea*, *Haemophilus influenzae*, *Acinetobacter baumannii*
- **Anaerobes:** *Bacteroides fragilis*, *Clostridium perfringens*, *Peptostreptococcus micros*, *Prevotella* spp.
- **Atypical bacteria:** *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*
- Indicated for cIAI and cSSSI
- Increased mortality as monotherapy in critically ill patients
New Areas of Research

1. Signal peptidase inhibition by arylomycins
   Large spectrum of activity and possible clinical applications
   Smith PA et al. Antimicrob Ag Chemother 2012;56:5054

2. Antibiotic hybrids

Summary

Gram negative strategies include

- Optimal dosing with extended infusion
- Combination treatment with available therapeutic agents
- Implementing empiric choices for critically ill, high risk patients
- Special access program for products commercialized in other countries
- Investigative options (phage therapy, novel agents)