Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. *Aspergillus fumigatus* is the leading cause of invasive aspergillosis (IA), a lethal infection among immunocompromised patients. Guideline-recommended antifungal therapy against IA is a triazole antifungal, with other secondary options including an echinocandin and amphotericin B. Concerns about drug-host toxicity and antifungal resistance have been globally reported, so new, safe, and effective therapeutics are imperative.

Methods. *In vitro*, CLSI standards were upheld as we tested APX2041, voriconazole, caspofungin, and amphotericin B against various *A. fumigatus* strains. *In vivo* we assessed toxicity and efficacy of APX2104 in immunocompromised mice respectively. Neutropenia was induced with 150 mg/kg of cyclophosphamide on days -2/+3 and 250 mg/kg of cortisone acetate on days -1/+6. Immunocompromised mice were infected in an inhalation chamber via 12 mL of aerosolized spores of *A. fumigatus* CEA10 at a concentration of $1x10^9$ spores/mL (Day 0). Treatment started day +1 and ended day +7.

Results. *In vitro*, APX2041, the active-form of APX2104, has over a 16-fold lower minimum effective concentration (MEC) when compared to voriconazole, caspofungin, and amphotericin B against various *A. fumigatus* strains, including echinocandin- and azole-resistant strains.

In vivo, given preliminary pharmacokinetic data, APX2104 was tested in non-infected immunocompromised mice at 60 mg/kg and 78 mg/kg once per day (QD). Deaths due to toxicity were seen only at a dose of 78 mg/kg, so 60 mg/kg was set as a safe dose for our *in vivo* efficacy studies. In IA-challenged neutropenic mice, treatment with either posaconazole (20 mg/kg BID) or APX2104 (60 mg/kg QD) equally prolonged survival in 14 of 15 (93%) mice 14 days post-infection (p= 0.985). Untreatment control yielded a survival of 3 of 15 (20%) 14 days post-infection (p= < 0.001). Consistent with our survival studies, H&E and GMS histological samples also demonstrated that APX2104 treatment decreased fungal burden within the lungs of neutropenic mice when compared to the untreated group.

Conclusion. Future studies will test the efficacy of APX2104 and posaconazole against azole antifungal resistant strains *in vivo*, as our preliminary findings suggest that APX2104 is a plausible solution to cure IA disease and combat antifungal resistance.

Disclosures. **All Authors**: No reported disclosures

1615. Isolation of Lytic Bacteriophages with Broad Host Range Activity Against *Pseudomonas aeruginosa* Strains Isolated from Respiratory Samples from Cystic Fibrosis Patients Intended for Therapeutic Application

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. With the rise of the antimicrobial resistance between different genera and species of bacteria, Phage Therapy is becoming a more realistic and accessible option for patients with limited or no antimicrobial options. Being able to have rapid access to a collection of clinical active phages is key for rapid implementation of phage therapy. The Microbiology Department at AdventHealth Orlando is performing routine screening of environmental and patient samples for isolation of phages against non-fermenting Gram negative bacteria to develop a Phage Bank.

Methods. Protocols for phage isolation from environmental sources such as lakes, rivers and sewers and clinical samples were developed. A series of respiratory, throat, stool and urine samples were processed following an internal protocol that includes centrifugation, filtration and enrichment. Clinical samples were centrifugated for 10 minutes, filtered using 0.45µm centrifugation filters, seeded with targeted host bacteria (clinical isolates) and incubated at 35°C for 24 hours. The enriched samples were centrifugated and filtered for a final phage enriched solution. Screening and isolation were performed using the Gracia method over trypticase soybean agar (TSA) for plaque morphology and quantification. Host range screening of other clinical isolates of *P. aeruginosa* was performed using the new isolated and purified phages.

Results. 4 lytic phages against clinical strains of *P. aeruginosa* from patient with diagnosis of cystic fibrosis (CF), were isolated and purified from 4 different respiratory samples, including sputum and bronchial alveolar lavage. All phages showed phenotypical characteristics of lytic activity. 1 phage was active against 4 strains of *P. aeruginosa*, 1 phage was active against 2 strains of *P. aeruginosa* and the remaining 2 phages were active only against the initial host target strain.

Conclusion. With this study we demonstrated the potential use of clinical samples as source for isolating active bacteriophages against clinically significant bacteria strains. Clinical samples from vulnerable population of patients with chronic infections are part of our routine "phage-hunting" process to stock and grow our Phage Bank project for future clinical use.

Disclosures. **All Authors**: No reported disclosures

1616. Mechanism of Thrombocytopenia Induced by Oxazolidinones Antibiotics (Linezolid, Tedizolid): Demonstration of Impairment of Megakaryocyte Differentiation From Human Hematopoietic Stem Cells associated with Mitochondrial Toxicity

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Linezolid causes thrombocytopenia, which limits its use. In cell culture and in tissues from treated patients, linezolid impairs mitochondrial protein synthesis (due to structural similarities and common binding sites between bacterial and mitochondrial ribosomes). Recent studies have shown that mitochondria act as a key relay in the process leading from activation of the thrombopoietin receptor to megakaryocytes differentiation.

Methods. Validated ex-vivo human model of hematopoietic stem cells (HSC) differentiation for (i) measuring megakaryocytes, granulocyte-monocytes, and burst-forming unit-erythroids colony formation; (ii) differentiation into megakaryocytes (conversion of CD34+ into CD41+/CD42+ cells; morphology) and proplatelets formation, (iii) mitochondrial toxicity (electron microscopy; cytochrome c-oxidase activity [partly encoded by the mitochondrial genome]).

Results. We show that linezolid (and the recently approved tedizolid), both at concentrations corresponding to their human serum concentrations) inhibit the maturation of HSC into fully differentiated megakaryocytes (CD41 and CD42-positive cells) and the formation of proplatelets. Optic and Electron microscopy) showed an impairment of the formation of typical megakaryocytes (lack of large polylobulated nuclei and of intracellular demarcation membrane system [required for platelet formation]), together with disappearance of the internal structure of mitochondria. Biochemical studies showed a complete suppression of the activity of cytochrome *c*-oxidase (a key enzyme of the mitochondrial respiratory chain).

Conclusion. Our study provides for the first time insights in the mechanism of thrombocytopenia induced by linezolid and tedizolid, identifying mitochondria as their target and showing that the drugs will impair the differentiation of hematopoietic stem cells into mature platelets-releasing megakaryocytes. It illustrates how mitochondria dysfunction may play a key role in toxicology and diseases, while paving the way for rational approaches for the design and screening of less toxic derivatives for the benefit of future patients.

Disclosures. **Paul M. Tulkens, MD, PhD**, **Bayer** (Consultant, Advisor or Review Panel member, Speaker's Bureau)**Menarini** (Speaker's Bureau)**Merck** (Advisor or Review Panel member, Speaker's Bureau)**Trius (now part of Merck)** (Advisor or Review Panel member, Research Grant or Support) **Françoise Van Bambeke, PharmD, PhD**, **Bayer** (Speaker's Bureau)

1617. Mecillinam susceptibility against Enterobacterales isolated from urinary tract infections from US patients in 2018

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Mecillinam is a unique amidinopenicillin antibiotic, being the first and the only compound in its class. In contrast to other beta-lactams, it has a unique mechanism of action whereby it exerts its antibacterial activity through binding to penicillin binding protein 2. Pivmecillinam is the oral-prodrug of mecillinam and recommended as a first line therapy in the IDSA guidelines for uncomplicated urinary tract infections (uUTI), despite not yet being available in the USA. To support the clinical development of mecillinam and pivmecillinam in the USA for the treatment of both complicated UTI and uUTI this study investigated the activity of mecillinam against Enterobacterales isolates from the USA during 2018.

Methods. A total of 1,090 isolates from urinary tract infections from patients in the USA were tested. Activity of antibiotics was tested by CLSI methodology and susceptibility interpreted according to CLSI guidelines.

Results. Susceptibility and activity of each antibiotic are shown in the Table. Mecillinam MIC_{50} and MIC_{90} were 0.25 and 4 µg/mL, respectively and 94.5% of isolates were susceptible. Fosfomycin MIC_{50} and MIC_{90} were 2 and 32 µg/mL, respectively and 95.7% of isolates were susceptible. The other four comparator antibiotics showed MIC_{90} values >8 µg/mL and a 70.5 – 79.9% susceptible isolates. The highest MIC_{90} against all isolates combined was 64 µg/mL for nitrofurantoin and the highest percentage of resistance was obtained with trimethoprim-sulfamethoxazole with 29.5%. Resistance towards ceftriaxone and ciprofloxacin was 19.6% and 26.1%, respectively.

Table

		Susceptibility			MIC (µg/mL)			
Drug	Breakpoints (S|I|R)	%S	%I	%R	MIC_{50}	MIC_{90}	MIN	MAX
MEC	**≤8 | 16 | ≥32**	**94.50**	**1.5**	**4.0**	**0.25**	**4**	**0.03**	**>128**
CRO	≤1 | 2 | ≥4	79.9	0.5	19.6	0.03	>8	≤0.015	>8
CIP	≤0.25 | 0.5 | ≥1	71.5	2.5	26.0	0.015	>8	≤0.002	>8
FOS	≤64 | 128 | ≥256	95.7	2.3	2.0	2	32	≤0.06	>256
NIT	≤32 | 64 | ≥128	70.6	19.8	9.5	16	64	≤2	>128
SXT (1:19)	≤2/38 | - | ≥4/76	70.5	-	29.5	0.12	>8	≤0.015	>8

MEC, mecillinam; CRO, ceftriaxone; CIP, ciprofloxacin; FOS, Fosfomycin; NIT, nitrofurantoin; SXT (1:19), trimethoprim / sulfamethoxazole (1:19)

Conclusion. Overall, mecillinam showed the lowest MIC_{90} and a comparable susceptibility profile (94.5 % susceptible and 4.0 % resistant) to fosfomycin (i.e. 95.7% and 2.0% resistant) susceptible isolates). Resistance to ceftriaxone, ciprofloxacin and trimethoprim/sulfamethoxazole around or above 20% is concerning for their clinical usage to treat urinary tract infections. These encouraging susceptibility data warrant

further studies to support the clinical development of mecillinam/pivmecillinam for the treatment of UTI in the USA.

Disclosures. Stephen Hawser, PhD, Tetraphase Pharmaceuticals (Scientific Research Study Investigator) Cedric Charrier, PhD, IHMA (Employee)Utility Therapeutics (Independent Contractor) Cyntia De Piano, PhD, IHMA (Employee) Utility Therapeutics (Independent Contractor) Morton Alexander, PhD, Utility Therapeutics (Employee, Shareholder) Anne Santerre Henriksen, MS, Maxel Consulting ApS (Employee)Utility Therapeutics (Independent Contractor)

1618. Meropenem-vaborbactam vs standard of care for multidrug resistant carbapenem-resistant Enterobacteriaceae

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Antimicrobial resistance to gram negative organisms is an increasing issue worldwide, particularly with regards to extended-spectrum B-lactamase (ESBL) and carbapenem-resistant *Enterobacteriaeceae* (CRE) producing organisms. Meropenem/vaborbactam (M-V) is an approved antimicrobial for treatment of some CRE infections. This study compares the outcomes of patients with CRE who were treated with M-V to standard of care (SoC) therapy.

Table 1. Results

Table 1. Results

	Treated with M-V (N=25)	Treated with SoC (N=25)	P value
Mean age (SD)	63	66	0.526
Female	36%	60%	0.156
Mean length of stay in days (SD)	33	32	0.899
Infection source			
Intraabdominal	56%	56%	
Pneumonia	24%	24%	-
Genitourinary	16%	16%	
Skin/Soft tissue	4%	4%	
Pathogen isolated			
Klebsiella pneumoniae	52%	48%	
Escherichia coli	20%	20%	
Enterobacter sp.	20%	16%	-
Citrobacter freundii	4%	8%	
Serratia marcescens	0	4%	
Other *Klebsiella sp.*	4%	4%	
30 day mortality	48%	32%	0.387
30 day re-admission	20%	16%	1
Clinical outcome			
Cure	52%	28%	0.148
Improved	**0%**	**40%**	**0.001**
Failure	48%	32%	0.098
Non-evaluable	0	0	-
Microbiological outcome			
Eradication	24%	4%	0.098
Presumed eradication	**28%**	**68%**	**0.01**
Persistence	8%	6%	1
Presumed persistence	40%	24%	0.364
	Treated with M-V (N=11)	**Treated with SoC (N=15)**	**P value**
Acute kidney injury*	16%	8%	1

[*AKI was defined as an occurrence of post-baseline Cr >1.5 times the baseline serum creatinine, from 48 hours post-therapy completion. A total of 14 patients were excluded in the M-V group, and 10 patients in the SoC group due to baseline Cr > 2.0.]

Methods: A retrospective chart analysis was performed which analyzed 25 patients in the M-V group and 25 patients in the SoC group at an 800-bed tertiary care hospital in Southeast Michigan. Patients were matched by type of infection. Variables included basic demographics, infection source, bacterial species, as well as 30-day re-admission, ICU admission, and creatinine pre- and post-treatment. The primary outcome of interest was 30-day mortality and clinical outcome (cure/improved/failure). Secondary outcomes included microbiological outcome (eradication/presumed eradication/persistence/presumed persistence) and acute kidney injury (AKI) on therapy. The data was analyzed using SPSS version 14.0.

Results. The most commonly used antibiotics in the SoC group were ceftazidime-avibactam (64%) and cefepime (32%). In both groups, the most common infection source was intra-abdominal (56%). The most commonly isolated pathogen in each group was *Klebsiella pneumoniae* (52% in M-V and 48% in SoC). Mortality and re-admission at 30 days did not differ statistically between the two groups. However, patients who received M-V were found to be more likely to achieve clinical cure, although this did not achieve statistical significance. Patients who were treated with SoC were significantly more likely to achieve an improved clinical outcome and presumed microbiological eradication (p=0.001 and 0.01 respectively). Of the 50 patients, only 26 patients (52%) met criteria to analyze for AKI. Patients who received M-V were more likely to have AKI (16% compared to 8%) but this did not reach statistical significance.

Conclusion. M-V is an important option for care of patients with infections due to MDR gram-negative bacteria. However, further studies are warranted to determine whether its use is associated with reduced mortality and improved clinical outcomes.

Disclosures. Marcus Zervos, MD, Melinta Therapeutics (Grant/Research Support)

1619. Meta-analysis of Randomized Control Trials Evaluating New Beta-Lactamase Combination Antibiotics

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Ceftolozane/ Tazobactam (C/T), Ceftazidime/ Avibactam (C/A), Meropenem/ Vaborbactam (M/V) and Imipenem/ Relebactam (I/R) are new combination beta-lactam/ beta-lactamase inhibitor antibiotics primarily used to treat multidrug-resistant (MDR) Gram-negative infections. This study synthesized outcomes of comparative observational studies and randomized control trials (RCTs) that evaluated clinical success of these antibiotics compared to other therapies.

Methods. PubMed, EMBASE, and Google Scholar were searched from January 1st, 2013 through October 1st, 2019 for comparative observational studies and RCTs of C/T, C/A, M/V and I/R in patients with pneumonia, complicated intra-abdominal and urinary tract infections. Study and patient demographics were collected along with clinical and microbiological success rates. Meta-regression analysis was used to determine the pooled effectiveness of C/T, C/A, M/V, and I/R. Heterogeneity and publication bias were assessed via I^2 values and funnel plots, respectively.

Results. Literature search returned 1,645 results. After exclusion criteria, 21 publications representing 6,246 patients were retained: 16 RCTs (8 C/A, 3 C/T, 3 I/R, 2 M/V) and 5 comparative observational studies (3 C/A, 2 C/T). Pooled risk ratios for clinical success showed that all four antibiotics were non-inferior to comparator antibiotics (0.99 (95% CI (0.97-1.01)). Eleven of the sixteen RCTs evaluated microbiological success; pooled risk ratio was 1.08 (95% CI 1.04-1.13), indicating that older therapies were more successful at microbiological eradication than newer antibiotics. Only 6 of the included studies (3 RCTs and 2 observational studies) focused on patients with MDR infections. Limiting the analysis to MDR RCTs did not change the overall conclusions.

Conclusion. Although older therapies had slightly higher microbiologic clearance, pooled clinical success rates for C/A, C/T, M/V, and I/R were non-inferior to older therapies, including in studies focused on patients with MDR infections. Additional studies are needed to further evaluate these drugs' effectiveness for treatment of MDR infections.

Disclosures. **All Authors**: No reported disclosures

1620. Minocycline Activity Against Unusual Clinically Significant Gram-Negative Pathogens

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Unusual non-glucose fermenting Gram-negative (NFGN) pathogens, including *Burkholderia cepacia* species complex, *Achromobacter spp*, *Alcaligenes spp, Aeromonas spp*, and other genera, can cause serious hospital-acquired infections in immunocompromised patients. Some genera are inherently resistant to common drug classes and can acquire other resistance mechanisms, making them difficult to treat. In this study, we analyzed the susceptibility of NFGN isolates to minocycline (MIN). Isolates were collected as part of the SENTRY Antimicrobial Surveillance Program from 2014-2019.

Methods. From 2014-2019, unusual NFGN isolates were collected from hospitalized patients in 102 hospitals in 35 countries on 4 continents. Hospitals submitted 1 isolate per patient per infection episode that met local criteria for being the likely causative pathogen. Identification was performed by the submitting laboratory and confirmed by JMI Laboratories with matrix-assisted laser desorption ionization-time of flight mass spectrometry or other molecular methods as required. Isolates were tested for MIN susceptibility using the CLSI broth microdilution method at JMI Laboratories. All infection types were included in the susceptibility analysis.

Results. The most common infection from which the NFGN were isolated was pneumonia. The top 5 NFGN species were *Achromobacter xylosoxidans* (n=202), *Burkholderia cepacia* species complex (n=199), unspeciated *Achromobacter* (n=190), *Aeromonas* spp (n=127), including *Aeromonas hydrophila* (n=35), *Chryseobacterium spp* (n=59), and *Alcaligenes faecalis* (n=42). The % susceptible and $MIC_{50/90}$ values of MIN for these species are shown in the table.

Conclusion. MIN had > 85% susceptible for the most frequently isolated unusual NFGN, including 92% susceptible for *Achromobacter* spp. and 85.9% for *B. cepacia*.