mortality was greater for patients with higher MICS (U=20.5, p=0.06). The presence of an underlying source may be related to recurrence of BSI (p=0.075).

Table 1: Patient Characteristics

	Daptomycin + β-Lactam (n= 23)	Other therapy (n= 62)	*P value*
Age, mean (SD)	58 (13)	52 (14)	0.142
Race, n (%)			
Black	5 (22)	27 (44)	0.065
Caucasian	**11 (48)**	**13 (21)**	**0.014**
Hispanic	7 (30)	22 (35)	0.662
Transplant Recipient, n (%)	**14 (61)**	**14 (23)**	**< 0.001**
Pitt Bacteremia Score, mean (SD)	5 (4)	4 (4)	0.087
Charlson Comorbidity Index, mean (SD)	**5 (3)**	**4 (3)**	**0.013**
VRE colonization, n (%)	14 (88)[a]	17 (63)[a]	0.083
Beta-lactam, n (%)			
Ampicillin	8 (35)	N/A	N/A
Ampicillin-sulbactam	3 (13)		
Ceftriaxone	3 (13)		
Cefepime	2 (9)		
Ertapenem	5 (22)		
Ceftaroline	2 (9)		
Daptomycin dose <8mg/kg, n (%)	1 (4)	2 (8)[b]	0.601
Daptomycin dose considered appropriate, n (%)	18 (78)	19 (76)[b]	0.852
MIC of Daptomycin via E-test, n (%)			
<1 µg/mL	1 (4)	1 (4)[b]	0.951
1-2 µg/mL	10 (43)	10 (40)[b]	0.807
3 µg/mL	8 (35)	7 (28)[b]	0.612
4 µg/mL	2 (9)	2 (8)[b]	0.930
≥6 µg/mL	0 (0)	0 (0)[b]	N/A
Unknown	2 (9)	5 (20)[b]	0.267
Primary Source, n (%)			
Blood	**8 (35)**	**38 (61)**	**0.029**
Primary Bacteremia	**3 (13)**	**25 (40)**	**0.017**
CLABSI	5 (22)	13 (21)	0.938
Other	**15 (65)**	**24 (39)**	**0.029**
Pulmonary	3 (13)	3 (5)	0.189
Gastrointestinal	7 (30)	14 (23)	0.455
Hepatic/Biliary	**3 (13)**	**0 (0)**	**0.027**
Urinary	2 (9)	7 (11)	0.729
Polymicrobial, n (%)	10 (43)	24 (39)	0.690

[a]n= 16, n= 27; 16 patients had VRE screening in the daptomycin plus beta-lactam group; 27 patients had VRE screening in the other therapy group

[b]n= 25; 25 patients received daptomycin in the other group **without** a beta-lactam that has previously been cited in the literature as demonstrating in-vitro activity against VRE when combined with daptomycin

Table 2. Primary and Secondary Outcomes

	Daptomycin + in-vitro β-Lactam (n = 23)	Other (n = 62)	*P* value
Days to microbiological cure, mean (SD)	5 (4)	4 (5)	0.213
Microbiological cure ≤3 days, n (%)	13 (56.5)	42 (67)	0.336
Duration of therapy in days, mean (SD)	23 (15)	15 (15)	**0.001**
Length of stay in days, mean (SD)	109 (67)	68 (67)	**0.007**
Length of ICU stay in days mean (SD)	35 (54)	33 (53)	**0.002**
In-patient 30-day mortality, n (%)	6 (26)	17 (27)	0.902
Infection-related mortality, n (%)	2 (8.7)	6 (9.68)	0.999
Recurrence within 30 days, n (%)	10 (43)	5 (8)	**< 0.001**

Conclusion: We did not find a significant difference in time-to-microbiological clearance, although patients treated with DAP and a β-lactam had higher CCI and PBS. These results are limited by retrospective design, small sample size, and potential selection bias. Prospective randomized studies are needed to further validate these findings.

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1612. Evaluation of the Use of Ceftolozane/Tazobactam for the Treatment of ESBL-producing *Enterobacterales* Infections Using International Data from SPECTRA (Study of Prescribing Patterns and Effectiveness of Ceftolozane/Tazobactam Real World Analysis)

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SPECTRA Study Group

Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. There is a paucity of data on outcomes of patients with severe ESBL-producing *Enterobacterales* infections treated with empiric or directed ceftolozane/tazobactam (C/T). This study looked at the treatment patterns and outcomes associated with C/T use in the treatment of ESBL-producing *Enterobacterales.*

Methods. Data were collected from an international cohort of 32 hospitals in 6 countries as part of SPECTRA, a retrospective multicenter database of C/T use globally, from 2016 – 2019. All adult patients with an ESBL positive *Enterobacterales* sterile site culture and treated with ≥ 48 hours of C/T were eligible. Outcomes assessed were clinical success, 30-day mortality from index event and readmission.

Results. There were 59 patients with 121 ESBL positive isolates. Blood and urine were the most common sites of infection at 19.8% each, followed by respiratory (18.2%). *E. coli* (50%) and *K. pneumoniae* (30%) were the most common pathogens. On average patients had 2 positive ESBL isolates; median 1; range 1-15. Most patients had the same infection site and ESBL pathogen, however 13 had multi-site ESBL pathogens identified and only 2 had polymicrobial ESBL pathogens. Septic shock was observed in 14 (24%) patients; 29 (49%) were in the ICU at the onset of infection. The most common comorbid conditions were immunocompromised hosts (37%) and cardiac disease (32%). 29% of patients were transplant recipients, and 28% had a CrCl < 50 ml/min. In most patients (71%), C/T was given as directed therapy (i.e., once culture results were available). C/T was given prior to culture results (i.e., as empiric therapy) in 17 (29%) patients, of which 77% had clinical success. C/T dose was 1.5 g in 49%. Only 2 of 10 patients with a respiratory source received the currently licensed 3 g dose. Overall, clinical success was observed in 36 (61%) patients. 30-day mortality was 12%. Readmissions occurred in 5%, of which 2 were infection related.

Conclusion. The role of newer non-carbapenem antibiotics in the treatment of severe ESBL infections is currently undefined. In a multinational patient database, C/T was found to be effective in severe infections caused by ESBL-producing *Enterobacterales*. Prospective studies are needed to further define the role of C/T in the setting of frequent drug-resistant Gram-negative pathogens.

Disclosures. Laura A. Puzniak, PhD, Merck (Employee) Matteo Bassetti, MD, Shionogi Inc. (Advisor or Review Panel member) Pamela Moise, PharmD, Merck & Co., Inc. (Employee, Shareholder) David Paterson, Accelerate (Speaker's Bureau) BioMerieux (Speaker's Bureau)BioMerieux (Advisor or Review Panel member)Entasis (Advisor or Review Panel member)Merck (Advisor or Review Panel member)Merck (Grant/Research Support)Merck (Speaker's Bureau)Pfizer (Speaker's Bureau)Shionogi & Co., Ltd. (Grant/Research Support)VenatoRx (Advisor or Review Panel member)

1613. Global 2018 Surveillance of Eravacycline Against Gram-negative Pathogens, Including Multi-drug Resistant Isolates

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Session: P-71. Treatment of Antimicrobial Resistant Infections

Background. Eravacycline (ERV) is a fully-synthetic, fluorocycline antibacterial approved by the FDA and EMA for treatment of complicated intra-abdominal infections (cIAI) in patients ≥18 years of age. The purpose of this study was to describe the *in vitro* activity of ERV against Gram-negative pathogens, including multi-drug resistant (MDR) isolates, collected in 2018.

Methods. Isolates were collected during 2018 from various body sites. Minimum inhibitory concentrations (MICs) were determined by CLSI broth microdilution. Antibiotic susceptibility was determined using the most updated CLSI breakpoints, except for ERV and tigecycline (TGC) where FDA breakpoints established in 2018 and 2005 respectively, were used. MDR was defined as resistance to ≥3 antibiotics from aztreonam, a carbapenem (meropenem or ertapenem [ETP]), cefepime/cefotaxime/ceftazidime/ceftriaxone (any one), gentamicin, levofloxacin, piperacillin-tazobactam TZP, tetracycline or TGC.

Results. Summary MIC data for ERV and select comparators are shown in the Table. ERV MIC_{90} for all-Enterobacteriaceae was 0.5 µg/ml and for MDR-Enterobacteriaceae was 1µg/ml. The susceptibilities for all-Enterobacteriaceae were 93%, 95%, 93% and 82% for ERV, TGC, ETP and TZP, respectively. ERV further demonstrated higher rates of susceptibility than ETP and TZP against MDR-Enterobateriaceae, 81% vs 71% vs 38%. ERV $MIC_{50/90}$ for carbapenem-resistant *Acinetobacter baumannii* (CRAB) were 4-fold lower than TGC.

Table

Organisms (N)	ERV $MIC_{50/90}$	TGC $MIC_{50/90}$	ETP $MIC_{50/90}$	TZP $MIC_{50/90}$
Enterobacteriaceae (3395)	0.25/0.5	0.5/2	0.015/0.5	2/128
C. freundii (463)	0.25/0.5	0.5/2	0.015/0.5	4/128
E. cloacae (509)	0.25/1	0.5/2	0.06/1	4/128
E. coli (515)	0.12/0.25	0.25/1	0.015/0.06	2/32
K. oxytoca (508)	0.25/0.25	0.25/2	0.015/0.03	2/>128
K. pneumoniae (535)	0.25/1	0.5/2	0.015/0.5	4/>128
MDR-Enterobacteriaceae (669)	0.25/1	0.5/2	0.25/8	64/>128
CRAB (496)	0.5/1	2/4	NT	>128/>128

Units in µg/mL; $MIC_{50/90}$ - minimum inhibitory concentration required to inhibit growth of 50/90% of isolates; NT - not tested

Conclusion. ERV *in vitro* activity was demonstrated and comparable susceptibility rates were observed for clinically important Gram-negative pathogens, including resistant isolates. Overall, ERV MIC_{90} values were 2- to 8- fold lower than TGC. this study further highlights the *in vitro* activity of ERV against Gram-negative pathogens identified in patients with cIAI.

Disclosures. Virgil Lijfrock, PharMD, Tetraphase (Employee) Steven Morgan, PharMD, Tetraphase Pharmaceuticals (Employee) Sara Hwang, PharMD, Tetraphase Pharmaceuticals (Employee) Ekaterina Efimova, PharMD, Tetraphase Pharmaceuticals (Employee) Kenneth Lawrence, PharmD, Tetraphase Pharmaceuticals (Employee) Stephen Hawser, PhD, Tetraphase Pharmaceuticals (Scientific Research Study Investigator) Ian Morrissey, PhD, Tetraphase Pharmaceuticals (Scientific Research Study Investigator)

1614. Gwt1 Inhibitor, APX2104, Protects Against Invasive Aspergillosis in Neutropenic Mouse Model

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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.

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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.

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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