bictegravir+emtricitabine+tenofovir alafenamide (BIC+FTC+TAF) and with dolutegravir and lamivudine (DTG+3TC). Here, viral breakthrough (VB) and resistance development were evaluated under alternating high and low drug exposures simulating variable adherence levels.

Methods. Wild-type HIV-1 (IIIb)-infected MT-2 cells were exposed to drug combinations and monitored for VB. Experiments alternated between high and low drug concentrations of either BIC+FTC+TAF or DTG+3TC (Table 1). Drug concentrations for each regimen were determined using human plasma-free adjusted clinical trough concentrations (C_{min}), at simulated C_{min} after missing 2 or 4 consecutive doses (C_{min}-2 and C_{min}-4) based on drug half-lives. Emergent HIV-1 were genotyped by deep sequencing and a 2% threshold.

Results. In these experiments, constant drug concentrations corresponding to full adherence (C_{min}) did not lead to VB. Using C_{min} concentrations for one week followed by constant C_{min}-2 exposures for 4 weeks, DTG+3TC had VB and emergence of M184V/I in reverse transcriptase (RT) but there was no VB for BIC+FTC+TAF. Using alternating drug exposures of C_{min} (weeks 1 and 3) and C_{min}-2 or C_{min} -4 (weeks 2, 4, and 5), VB was not observed with BIC+FTC+TAF, and VB was decreased or delayed with DTG+3TC compared to DTG+3TC held at C_{min}-2 or C_{min}-4. Resistance development was observed in some cultures with VB: 1 culture with BIC+FTC+TAF had G163R in IN and 19 cultures with DTG+3TC had INSTI and RT resistance including 10 with M184V/I.

Table 1. Summary of Breakthrough Frequency and Resistance Development

In Vitro Dosing (By Week)					Breakthrough Frequency (Resistance Development)			
					BIC+FTC+TAF		DTG+3TC	
Week 1	Week 2	Week 3	Week 4	Week 5	VB (n/N,%)	With Resistance (n)[c]	VB (n/N,%)	With Resistance (n)[c]
Cmin [a]					0/60; 0	0	9/60; 15	Other (3)
Cmin					0/12; 0	0	0/12; 0	0
Cmin-2 [a]					0/60; 0	0	54/60; 90	M184V/I (4/7) [b]
Cmin	Cmin-2				0/12; 0	0	7/12; 58	M184I (1/2) [b]
Cmin	Cmin-2	Cmin	Cmin-2		0/12; 0	0	0/12; 0	0
Cmin-4					31/36; 86	Other (1/1) [b]	36/36; 100	M184I (1/3) [b]
Cmin	Cmin-4	Cmin	Cmin-4		0/12; 0	0	12/12; 100	M184I (4/4)

[a] Previously determined data; [b] Other mutations were G163R in integrase for BIC+FTC+TAF and V75I, V118I, T215A/I, and K219N/R in reverse transcriptase and M50I, L74M, A128T, G140E, P145S, S153F, E157K, and R263K in integrase for DTG+3TC; [c] (number of cultures with M184V/I/number of cultures with emergent resistance)

Conclusion. BIC+FTC+TAF has high *in vitro* forgiveness and consistent protection against emergence of drug resistance during simulations of short lapses in adherence. Higher DTG+3TC exposure, whether constant or intermittent, was better at preventing or delaying VB than lower DTG+3TC exposures, but DTG+3TC was less forgiving than BIC+FTC+TAF. Prevention of viral replication and resistance development is necessary to maintain lifelong viral suppression, particularly in the real world where drug adherence is often imperfect.

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1449. Frequency and Antimicrobial Susceptibility of Coagulase-Negative Staphylococcal (CoNS) Species Isolated from Clinical Specimens in United States and European Hospitals

Helio S. Sader, MD, PhD[1]; Cecilia G. Carvalhaes, MD, PhD[2]; Jennifer M. Streit, BS[1]; S. J. Ryan Arends, PhD[1]; Rodrigo E. Mendes, PhD[1]; [1]JMI Laboratories, North Liberty, Iowa; [2]JMI Laboratories, Inc., North Liberty, Iowa

Session: P-66. Resistance Mechanisms

Background. CoNS represent an important cause of bloodstream infections, osteoarticular infections, foreign-body-associated infections and endocarditis. We evaluated the frequency of CoNS species and the activity of dalbavancin (DALB) in comparison to vancomycin (VAN), daptomycin (DAP) and other agents against a large collection of CoNS isolates.

Methods. 5,088 CoNS isolates causing clinically significant infection were consecutively collected from 122 medical centers located in the United States (79 centers) and Europe (43 centers in 21 nations) over 6 years (2014-2019) and susceptibility tested by CLSI broth microdilution methods against DALB and comparators. Species identification was confirmed by MALDI-TOF.

Results. Most isolates were from bloodstream (BSI; 53.5%) or skin/skin structure infections (28.5%). *S. epidermidis* was the most common species overall (54.6%; Table) and for BSI (61.3%). The second most common species were *S. lugdunensis* overall (12.3%) and *S. hominis* for BSI (14.7%). DALB ($MIC_{50/90}$, 0.03/0.06 mg/L) inhibited > 99.9% of CoNS isolates at the susceptible (S) breakpoint established by CLSI for *S. aureus* (≤ 0.25 mg/L) and was 8-fold more active than DAP ($MIC_{50/90}$, 0.25/0.5 mg/L; 99.9% S) and 32-fold more active than VAN ($MIC_{50/90}$, 1/2 mg/L; > 99.9% S). Linezolid was active against 98.7% of isolates ($MIC_{50/90}$, 0.5/1 mg/L). All species were inhibited at ≤0.25 mg/L of DALB, except *S. epidermidis* (> 99.9%) and *S. warneri* (98.9%; Table). The most DALB-S species were *S. capitis* and *S. simulans* ($MIC_{50/90}$, 0.015/0.03 mg/L for both species), whereas the highest DALB $MIC_{50/90}$ values were observed with *S. haemolyticus* and *S. saprophyticus* ($MIC_{50/90}$, 0.06/0.12 mg/L and highest MIC of 0.25 mg/L for both species). In contrast, 47.8% of *S. epidermidis* and 34.7% *S. haemolyticus* exhibited decreased susceptibility to VAN (MIC ≥ 2 mg/L), and 23.2% of *S. capitis* and 28.4% of *S. warneri* showed decreased susceptibility to DAP (MIC ≥ 1 mg/L). Overall oxacillin-S rate was 39.3%, varying from 3.0% for *S. saprophyticus* to 95.4% for *S. lugdunensis*. In general, BSI isolates were slightly less S than non-BSI isolates.

Conclusion. Antimicrobial susceptibility varied widely among CoNS species. DALB exhibited potent *in vitro* activity against all CoNS species.

Table 1

Species / no. tested overall	Cumulative % at DALB MIC of: 0.015	0.03	0.06	0.12	0.25[a]	DALB $MIC_{50/90}$	% at VAN MIC ≥2 mg/L	% at DAP MIC ≥1 mg/L
S. epidermidis (2,777)	21.1	76.2	96.1	99.5	>99.9	0.03/0.06	47.8	2.5
S. lugdenensis (625)	34.9	95.5	99.8	100.0		0.03/0.03	0.5	0.6
S. haemolyticus (449)	4.2	17.6	61.5	95.8	100.0	0.06/0.12	34.7	3.6
S. hominis (462)	33.3	86.6	98.3	100.0		0.03/0.06	9.6	0.6
S. capitis (267)	68.2	93.6	99.3	99.6	100.0	0.015/0.03	8.2	23.2
S. saprophyticus (169)	1.2	10.7	50.3	95.9	100.0	0.06/0.12	13.6	5.3
S. warneri (88)	35.2	70.5	90.9	97.7	98.9	0.03/0.06	8.0	28.4
S. simulans (65)	56.6	96.1	100.0			0.015/0.03	0.0	0.0
Other species (175)	40.6	77.1	94.3	98.9	100.0	0.03/0.06	6.9	11.4
All CoNS (5,088)	25.7	73.3	92.3	99.1	>99.9	0.03/0.06	33.9	4.8

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1450. Frequency of Carbapenem-resistant *Pseudomonas aeruginosa* Among Respiratory Pathogens Impacts First-Line Beta-Lactam Susceptibility: Potential Role for Ceftolozane/Tazobactam (C/T) and/or Imipenem/Relebactam (I/R)

Kenneth Klinker, PharmD[1]; Daryl DePestel, PharmD, BCPS-ID[1]; Mary Motyl, PhD[2]; C. Andrew DeRyke, PharmD[2]; [1]Merck & Co, Inc, Kenilworth, New Jersey; [2]Merck & Co., Inc., Kenilworth, NJ

Session: P-66. Resistance Mechanisms

Background. Carbapenem-resistant *P. aeruginosa* (CRPA) are associated with increased mortality and impose significant treatment challenges for clinicians. Among CRPA, co-resistance to 1st line antipseudomonal agents piperacillin/tazobactam (TZP) and cefepime (FEP) is common and often results in delays to timely effective therapy. A simple strategy for identifying patients at risk for suboptimal therapy is evaluation of institutional or unit specific frequency of CRPA. The purpose of this analysis is to identify beta-lactam (BL) susceptibility trends based on CRPA frequency observed in intensive care units (ICU).

Methods. In 2016-2019, ~20 US institutions per year submitted up to 250 consecutive, aerobic or facultatively anaerobic, gram-negative pathogens from blood, intra-abdominal, urinary, and lower respiratory tract infections as part of the Study for Monitoring Antimicrobial Resistance Trends. A total of 871 *P. aeruginosa* (PA) isolates were collected from lower respiratory tract specimens obtained from ICU patients. MICs were determined using CLSI broth microdilution method and interpreted with CLSI 2020 or FDA breakpoints. Institutions were then stratified into one of three categories based on CRPA frequency: CRPA rates ≤20% (CR1), 21 – 40% (CR2), and ≥41% (CR3). BL susceptibility was then evaluated relative to CRPA frequency.

Results. Thirty-seven (46%), 25 (31%), and 18 (23%) institutions were stratified into CR1, CR2, and CR3, respectively. Overall, CRPA was identified in 28.4% of all