Conclusion. A host gene expression test discriminated bacterial, viral, and non-infectious etiologies at a lower overall accuracy in IC patients compared to immunocompetent patients, though this difference was only significant for bacterial vs non-bacterial disease. With modified interpretive criteria, a host response strategy may offer clinically useful and complementary diagnostic information for IC patients.

Disclosures. Thomas W. Burke, PhD, Predigen, Inc (Consultant) Geoffrey S. Ginsburg, MD PhD, Predigen, Inc (Shareholder, Other Financial or Material Support) Christopher W. Woods, MD, MPH, FIDSA, Predigen, Inc (Shareholder, Other Financial or Material Support) Ephraim L. Tsalik, MD, MHS, PhD, FIDSA, Predigen, Inc (Scientific Research Study Investigator, Shareholder, Other Financial or Material Support)

1227. Plazomicin Susceptibility Testing using ETEST® MIC for *Enterobacterales*

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Session: P-55. New Approaches to Diagnostics

Background. Plazomicin (PLZ) approved by FDA in June of 2018, is an aminoglycoside class antibacterial indicated for the treatment of adults with complicated urinary tract infections (cUTI) including pyelonephritis caused by Enterobacterales. It is used in patients who have limited or no alternative treatment options, e.g. CRE and MDRO patients. The drug has bactericidal activity, it is active against organisms producing ESBL, Carbapenemase and aminoglycoside-modifying enzymes. The purpose of this study was to compare ETEST® PLZ bioMérieux to the broth microdilution reference method (BMD) for *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca and pneumoniae, Morganella morganii, Providencia stuartii, Proteus mirabilis and vulgaris* and *Serratia marcescens* isolates.

Methods. A total of 598 isolates were tested by ETEST® (PLZ) and BMD at four clinical trial sites.

Isolates were subcultured on tryptic soy or Columbia agar plates supplemented with 5% sheep blood. Suspensions of the isolates were prepared in 0.85% saline, which were used to inoculate BMD and Mueller Hinton agar for ETEST®. Results were read after 16-20 hours incubation at 35°C +2°C in ambient air. QC organisms were tested with each run following CLSI QC guidelines.

Results were analyzed using FDA breakpoints for PLZ (Susceptible <2 µg/mL, Intermediate 4 µg/mL, Resistant >8 µg/mL).

Performance was evaluated using FDA performance criteria, EA and CA (≥ 90%), major error rate (≤3.0%) and very major error rate (≤2.0%).

Results.

Table 1. Performance for Plazomicin ETEST® PLZ for Enterobacterales

EA	CA	Very Major Error Rate	Major Error Rate	Minor Error Rate
99.0% (592/598)	92.8% (555/598)	1.9% (1/53)	0.0% (0/478)	7.0% (42/598)

Table 2. MIC distribution BMD and ETEST® PLZ (mode MIC in bold)

MIC/ Interp µg/ml	≤0.016 S	0.032 S	0.064 S	0.125 S	0.25 S	0.5 S	1 S	2 S	4 I	8 R	16 R	32 R	64 R	128 R	≥256R
BMD	0	0	0	5	122	172	98	81	67	15	7	1	0	1	29
ETEST® PLZ	0	0	0	5	59	232	93	94	65	11	7	3	0	0	30

Conclusion: ETEST® PLZ clinical performance met the FDA acceptance criteria and was found useful for determining Plazomicin MIC of Enterobacterales, including ESBL, CRE (MBL, KPC, Oxa-48), high level AmpC and aminoglycoside resistant strains. Percent susceptibility of Plazomicin is at 80% among the 598 isolates tested, the mode MIC is 0.5 ug/ml as Susceptible.

Disclosures. Tom Armstrong, BS, bioMérieux (Employee) Laurine Blanchard, PhD, bioMérieux (Employee) Michael Kresken, PhD, bioMérieux (Scientific Research Study Investigator, Research Grant or Support) Gilles Zambardi, biomerieux (Employee) Marion Pompilio, BioMérieux (Employee)

1228. The Role of Procalcitonin (PCT) and Lactic Acid in Febrile Neutropenic Cancer Patients in an Oncological Emergency Center

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Session: P-55. New Approaches to Diagnostics

Background. Procalcitonin (PCT) and lactic acid have emerged as biomarkers that increase in bacterial infections/sepsis and have been used in conjunction with clinical judgment to guide antibiotic administration. The Multinational Association for Supportive Care in Cancer (MASCC) risk index has been used to classify the risk for patients with neutropenic fever. However this index includes subjective elements and complex metrics that make it difficult to use in an oncological emergency center (EC). The purpose of this study is to evaluate the role of serum PCT alone and in combination with lactate to predict bloodstream infections (BSI), hospitalization and 14 days mortality in febrile neutropenic cancer patients presenting to the EC.

Methods. We conducted a retrospective study of all febrile neutropenic cancer patients who presented to our EC between April 1, 2018 and April 30, 2019 and had a serum PCT and lactic acid levels done. Fever was defined either as a documented temperature of ≥100.4 °F or a chief complaint of fever reported at home. Neutropenia was defined as an absolute neutrophil count ≤500 cells/mL.

Results. We included 550 cancer patients of which 385 (70%) had hematologic malignancies and 165 (30%) had solid tumors. A BSI was documented in 116 (21%) patients due to gram negative organisms in 66%, gram positive organisms in 30%, and both in 4%. A higher rate of mortality within 14 days of EC presentation was seen in patients whose PCT ≥ 0.25 compared to those with PCT < 0.25 (5.2% vs 0.7%; p=0.002). Similarly a higher rate of BSI and a longer hospital stay was seen in patients whose PCT ≥ 0.25 compared to those with PCT < 0.25. A PCT ≥ 0.25 or a lactate level >2.2 had a sensitivity of 93% and a negative predictive value of 100% for a 14 day mortality. A logistic regression analysis showed an association between BSI and hematological malignancy, PCT ≥ 0.25, and lacate level >2.2 mmole/L.

Conclusion. A PCT ≥ 0.25 was associated with BSI, LOS and 14 day mortality. The combination of PCT / serum lactate have a good sensitivity and high negative predictive value for BSI and mortality. Because this combination could be useful in identifying the high risk febrile patients requiring hospital admission, it will be compared to the standard but more labor intensive MASCC score index.

Disclosures. **Issam I. Raad, MD, Citius** (Other Financial or Material Support, Ownership interest)**Cook Medical** (Grant/Research Support)**Inventive Protocol** (Other Financial or Material Support, Ownership interest)**Novel Anti-Infective Technologies** (Shareholder, Other Financial or Material Support, Ownership interest)

1229. Volatile Biomarkers of Influenza Infection in the Breath

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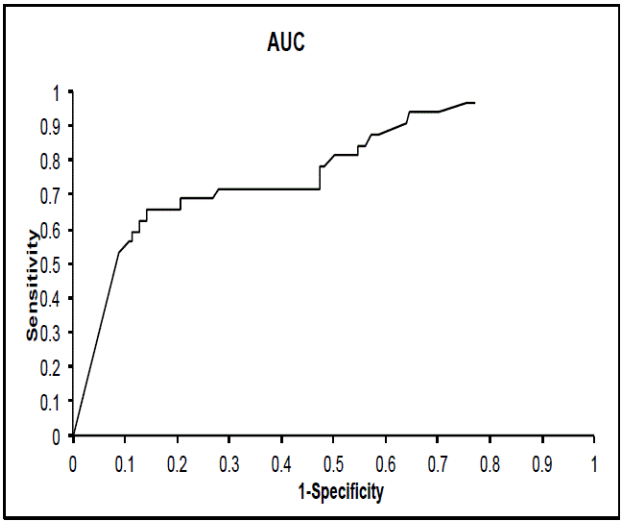
Session: P-55. New Approaches to Diagnostics

Background. Annual influenza epidemics cause significant morbidity and mortality. New, emerging strains threaten to cause catastrophic pandemics. Assay of exhaled breath for volatile organic compounds (VOCs) via gas chromatography-mass spectroscopy (GC-MS) is an emerging diagnostic modality ideally suited to fill the gap in influenza diagnostics.

Methods. Patients with influenza like illness (ILI) presenting to the Troop Medical Clinic on JBSA Fort Sam Houston, TX, from 3/2017 to 3/2019 submitted a 2-minute breath sample in addition to a nasopharyngeal swab collected for polymerase chain reaction (PCR) assay for influenza virus. ILI was defined as temperature > 100.4^0F AND respiratory symptoms like cough, sputum production, chest pain and/or sore throat. Breath VOCs were assayed with GC-MS and data were analyzed in order to identify the significant breath VOC biomarkers that discriminated between ILI patients with and without a PCR assay positive for influenza with greater than random accuracy.

Results. Demographic, clinical, PCR and breath data were available for 237 episodes of ILI. PCR was positive for influenza for 32 episodes (30 influenza A and 2 B). The median age of participants was 21 (IQR 19, 23) and 69% were male. There were no differences in age, gender, education, race, or smoking, between the influenza positive and negative groups. Likewise, there was no difference in days of limited activity or missed work, or symptoms at presentation between the groups. The algorithm achieved near maximal predictive accuracy of 78% with four biomarkers (74% sensitivity and 70% specificity). Based on their mass spectra, these biomarker VOCs were tentatively identified as 2-amino-1-propanol, 2-butanamine, n-nitro, 3-methyl-hexanal, and heptane, which are consistent with products of oxidative stress.

Figure. Accuracy, Sensitivity, and Specificity of Influenza Breath Test. Receiver operating characteristic (ROC) of the breath test (sensitivity versus 1-specificity). The accuracy of the breath test was 78%. With a cutoff point at the "shoulder" of the ROC curve, the test had 74% sensitivity and 70% specificity.



Conclusion. Our findings bolster available benchtop and clinical data suggesting that breath testing may be a useful diagnostic modality for influenza infection. The next step will be to study the predictive algorithm developed in this protocol in a blinded validation cohort. If the predictive algorithm performs well in a validation study, adaptation for its use in a portable, tabletop GC would be warranted to allow for a rapid, accurate, universal point-of-care influenza diagnostic test.

Disclosures. Michael Phillips, MD, Menssana Research, Inc (Grant/Research Support)

1230. Clinical and Microbiologic Outcomes by Causative Pathogen in Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia (HABP/VABP) Treated with Imipenem/Cilastatin (IMI)/Relebactam (REL) Versus Piperacillin/Tazobactam (PIP/TAZ)

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Session: P-56. New Drug Development

Background. IMI/REL is a combination of IMI and the novel class A and class C β-lactamase inhibitor REL. Here we present per-pathogen outcomes from a recent phase 3 clinical trial (RESTORE-IMI 2), in which IMI/REL was shown to be non-inferior to piperacillin/tazobactam (PIP/TAZ) for empiric therapy of HABP/VABP, in both primary and key secondary endpoints.

Methods. Randomized, controlled, double-blind, multinational, phase 3, non-inferiority trial in adults with HABP/VABP. Lower respiratory tract specimens were obtained ≤48 hours prior to screening. Participants (pts) were randomized 1:1 to IMI/REL 500 mg/250 mg or PIP/TAZ 4 g/500 mg, given intravenously every 6 h for 7-14 d. Pts also received empiric linezolid until baseline cultures confirmed absence of MRSA. This analysis evaluated outcomes by causative LRT pathogen in modified intent to treat (MITT) pts (randomized pts with ≥1 dose of study drug, excluding pts with only gram-positive cocci present on baseline Gram stain) who had ≥1 baseline LRT pathogen susceptible (according to CLSI criteria) to both study drugs. Outcomes assessed were microbiologic response at end of therapy (EOT), clinical response at early follow-up (EFU; 7-14 d after EOT), and Day 28 all-cause mortality (ACM).

Results. Of 531 MITT pts, 51.4% (130 IMI/REL, 143 PIP/TAZ) had ≥1 baseline LRT pathogen susceptible to both study drugs. The most common causative pathogens in this analysis population were *Klebsiella* spp (30.4% of patients), *Pseudomonas aeruginosa* (22.3%), *Escherichia coli* (22.0%), and *Haemophilus influenzae* (9.2%), consistent with other recent trials in HABP/VABP and with surveillance data. Outcomes by pathogen were generally comparable between IMI/REL and PIP/TAZ (Table). In a separate subgroup analysis of the microbiologic MITT population, in pts with ≥1 ESBL-positive LRT pathogen (45 IMI/REL, 35 PIP/TAZ), microbiologic response at EOT was 82.2% (IMI/REL) vs 68.6%% (PIP/TAZ), clinical response at EFU was 64.4% vs 60.0%, and Day 28 ACM was 20.0% and 22.9%, respectively. In the IMI/REL arm, 8 pts had ≥1 confirmed KPC-positive baseline LRT pathogen; KPC status was not assessed in the PIP/TAZ arm.

Conclusion. IMI/REL is an efficacious treatment option for HABP/VABP, regardless of causative pathogen.

Table. Primary and secondary efficacy outcomes in patients who were in the MITT population and had at least 1 baseline LRT pathogen susceptible to both study drugs

Baseline LRT Pathogen	Microbiologic Response at EOT		Clinical Response at EFU		Day 28 All-Cause Mortality	
	IMI/REL n/N (%)	PIP/TAZ n/N (%)	IMI/REL n/N (%)	PIP/TAZ n/N (%)	IMI/REL n/N (%)	PIP/TAZ n/N (%)
Enterobacterales overall	78/97 (80.4%)	72/100 (72.0%)	62/97 (63.9%)	62/100 (62.0%)	13/97 (13.4%)	22/100 (22.0%)
Klebsiella spp.[a]	32/42 (76.2%)	30/41 (73.2%)	25/42 (59.5%)	28/41 (68.3%)	6/42 (14.3%)	8/41 (19.5%)
E. coli	25/27 (92.6%)	23/33 (69.7%)	16/27 (59.3%)	19/33 (57.6%)	5/27 (18.5%)	8/33 (24.2%)
S. marcescens	8/10 (80.0%)	1/4 (25.0%)	7/10 (70.0%)	3/4 (75.0%)	2/10 (20.0%)	1/4 (25.0%)
E. cloacae	6/7 (85.7%)	13/16 (81.3%)	6/7 (85.7%)	12/16 (75.0%)	1/7 (14.3%)	3/16 (18.8%)
P. aeruginosa	17/26 (65.4%)	22/35 (62.9%)	12/26 (46.2%)	20/35 (57.1%)	7/26 (26.9%)	5/35 (14.3%)
A. calcoaceticus-baumannii complex	4/5 (80.0%)	4/10 (40.0%)	4/5 (80.0%)	6/10 (60.0%)	0/5 (0.0%)	1/10 (10.0%)
H. influenzae	12/13 (92.3%)	9/12 (75.0%)	9/13 (69.2%)	8/12 (66.7%)	2/13 (15.4%)	3/12 (25.0%)

[a]*Klebsiella* spp. includes *Klebsiella aerogenes*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae*.

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1231. VIR-2482: A potent and broadly neutralizing antibody for the prophylaxis of influenza A illness

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Session: P-56. New Drug Development

Background. Influenza A viruses are responsible for seasonal epidemics and represent a constant pandemic threat. Influenza vaccines induce predominantly antibodies against the head region of hemagglutinin (HA) and are strain specific. Vaccine effectiveness is often suboptimal due to mismatch with drifting viruses and an inadequate immune response. Broadly neutralizing monoclonal antibodies (mAbs) targeting the conserved stem-region of HA may provide protection through multiple seasons and cover strains with pandemic potential. We report pre-clinical data on VIR-2482, a fully human anti-HA stem mAb with half-life extending Fc mutations.

Methods. Binding of VIR-2482 to a panel of influenza HAs and neutralization of H1N1 and H3N2 viruses were measured by ELISA and microneutralization. Epitope conservation was evaluated using 49,462 HA sequences retrieved from GiSAID. Engagement of human FcγRs by VIR-2482 was assessed by biolayer interferometry. Antibody-dependendent cell-mediated cytoxicity (ADCC) was measured via in vitro killing of A549 cells expressing H1-HA glycoprotein by human NK cells. Complement-dependent cytotoxicity (CDC) was evaluated by incubating VIR-2482 with H1N1 infected cells in the presence of guinea pig complement. Protection studies were performed in Balb/c mice given VIR-2482 24h before intranasal infection with a lethal dose of H1N1 PR8 and H3N2 HK/68.

Results. VIR-2482 binds to the HA proteins representing all 18 influenza A HA subtypes and neutralizes a broad panel of H1N1 and H3N2 viruses spanning almost 100 years of evolution. Bioinformatic analysis revealed >98.8% conservation for the majority of key contact residues examined from sequences retrieved for H1N1 and H3N2 between 2009-2019. The half-life extending mutations in the Fc portion do not affect the ability of the antibody to engage FcγRIIIa, FcγRIIa, and C1q as evidenced by their lack of impact on ADCC and CDC in vitro. Prophylactic administration of VIR-2482 protects Balb/c mice from infection with lethal challenge doses of H1N1 and H3N2 viruses.

Conclusion. The attributes of potency, broad recognition of a highly conserved epitope, retention of high-level effector functions in addition to half-life extension support the development of VIR-2482 as a universal prophylactic for influenza A illness.

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