657. Evaluation of Nanopore-Based 16S Ribosomal RNA (rRNA) Gene Sequencing for the Development of a Rapid Infection Intervention Clinical Service

Rahul Batra, MD[1]; R. Baldan, PhD[1]; P. Cliff, PhD[2]; Amita Patel[1]; Jonathan Edgeworth, PhD, FRCPath[1]; M. Chand, PhD, FRCPath[1]; [1]Guy's and St Thomas' NHS Foundation Trust, London; [2]Viapath LLC, London, UK

Session: 67. New Diagnostics

Thursday, October 3, 2019: 12:15 PM

Background. Rapid and accurate identification of bacteria is the basis of appropriate antibiotic treatment and effective clinical decision-making. Next-generation sequencing (NGS) platforms such as Oxford Nanopore Technologies (ONT) holds the promise of a diagnostic revolution by overcoming the limitations of culture-based identification with rapid molecular detection of bacteria. We have developed a pilot to evaluate an ONT 16S rRNA gene assay with the ability to provide real-time analysis and identification of bacterial species. Our aim was to investigate whether long-read sequencing and high-speed analysis can be combined to create a clinically useful, rapid diagnostic tool.

Methods. A collection of bacterial isolates representing pathogenic species received by the clinical laboratory over 1 year was assembled. Sample preparation was as described in the ONT 16S protocol and included bead beating sample disruption, MagNA Pure automated nucleic acid extraction (Roche), and PCR amplification (Thermo). Sequencing was performed on the MinION and GridION X5 platforms. Output was analyzed with ONT's automated EPI2ME 16S pipeline which assigns reads to taxa using BLAST results and the NCBI 16S Bacterial database.

Results. A total of 155 clinical samples with 139 species were sequenced. 119 species were identified at the species level. For 20 samples, a species in the same genus claimed the majority of reads, with the true species being matched to 3%-41% of reads. The average proportion of reads assigned to the correct species was 62.2%, specifically 67% for non-Enterobacteriaceae and 33% for Enterobacteriaceae. 4 clinical samples (3 Bronchoalveolar lavages (BALs), positive for (1) *K. pneumoniae*, (2) *S. pneumoniae*, and (3) *S. pneumoniae*, *S. enterica*, and *S. typhimurium*, and 1 bone positive for *P. aeruginosa*) were also analyzed with sequencing results matching culture.

Conclusion. Early results show that 16S rRNA sequencing coupled with real-time analysis was able to accelerate pathogen detection and was able to discriminate the majority of species from a relevant clinical collection. Pipeline refinement is required and subsequent confirmatory consensus-based identification may be a helpful adjunct. Nanopore sequencing shows promise as a rapid bacterial pathogen detection platform for clinical service.

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

658. Cost-effectiveness of Molecular Diagnostic Assays for the Therapy of Severe Sepsis and Septic Shock in the Emergency Department

Ioannis Zacharioudakis, MD[1]; Fainareti Zervou, MD[1]; Fadi Shehadeh, M. Eng.[2]; Eleftherios Mylonakis, MD PhD[2]; Eleftherios Mylonakis, MD PhD[2]; [1]New York University, Long Island City, New York; [2]Brown University, Providence, Rhode Island

Session: 67. New Diagnostics

Thursday, October 3, 2019: 12:15 PM

Background. Sepsis presents a major burden to the emergency department (ED). Because empiric inappropriate antimicrobial therapy (IAAT) is associated with increased mortality, rapid molecular assays may decrease IAAT and improve outcomes.We evaluated the cost-effectiveness of molecular testing as an adjunct to blood cultures in patients with severe sepsis or septic shock evaluated in the ED.

Methods. We developed a decision analysis model with the primary outcome the incremental cost-effectiveness ratio expressed in terms of deaths averted. Costs were dependent on the assay price and the patients' length of stay (LOS). Three base-case scenarios regarding the difference in LOS between patients receiving appropriate (AAT) and IAAT were described.Sensitivity analyses regarding the assay cost and sensitivity, and its ability to guide changes from IAAT to AAT were performed.

Results. Under baseline assumptions, molecular testing was cost-saving when the LOS differed by 4 days between patients receiving IAAT and AAT (ICER −$7,302/death averted). Our results remained robust in sensitivity analyses for assay sensitivity ≥52%, panel efficiency ≥39%, and assay cost ≤$270. In the extreme case that the LOS of patients receiving AAT and IAAT was the same, the ICER remained ≤$20,000/death averted for every studied sensitivity (i.e., 0.5–0.95), panel efficiency ≥34%, and assay cost ≤$313. For 2 days difference in LOS, the bundle approach was dominant when the assay cost was ≤$135 and the panel efficiency was ≥77%.

Conclusion. The incorporation of molecular tests in the management of sepsis in the ED has the potential to improve outcomes and be cost-effective for a wide range of clinical scenarios.

Disclosures. Eleftherios Mylonakis, MD PhD, Sanofi-Pasteur: Grant/Research Support; T2 Biosystems: Grant/Research Support.

659. Evaluation of a Rapid Diagnostic Assay for Early Detection of Bacteriuria

Robbie Lee Anne. Christian, PharmD[1]; Curtis Donskey, MD[2]; Maria Navas, MD D (ABMM)[3]; [1]Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio; [2]Cleveland VA Medical Center, Cleveland, Ohio; [3]VA Northeast Ohio Healthcare System, Cleveland, Ohio

Session: 67. New Diagnostics

Thursday, October 3, 2019: 12:15 PM

Background. Patients with suspected urinary tract infection (UTI) are often prescribed an empiric antibiotic treatment due to delays in obtaining results of urine cultures. The BacterioScan System measures the turbidity of incubating urine specimens to provide a qualitative determination of bacteriuria at a density of >5 × 10^4 colony-forming units (CFU)/mL within approximately 3 hours. We examined the utility of the BacterioScan assay in predicting bacteriuria and assessed the potential impact of this test to reduce the number of urine cultures processed.

Methods. Urine samples received for culture in the microbiology laboratory of the Cleveland VA Medical Center were collected daily between September 2018 and December 2018. For each specimen, we performed a bacterioscan diagnostic test and compared it with the result of the traditional culture and urinalysis if available. Urinary cultures were categorized into 4 groups as defined in Figure 1. We compared the sensitivity and specificity of the bacterioscan vs. urinalysis (leukocyte esterase and/or pyuria) results.

Results. 120 urine samples were tested. As shown in Table 1, the BacterioScan had better sensitivity and specificity than the urinalysis for detection of positive urine cultures. The use of the BacterioScan to rule out UTI could have accurately spared 69 of 120 (57.5%) samples from traditional culture and prevented 26 of 120 (21.6%) from possible misinterpretation as infection due to reporting of growth. BacterioScan resulted in 4 of 31 (12.9%) false negatives, but all occurred when positive cultures were due to viridans streptococci or uropathogens in numbers below 100,000 CFU.ml.

Conclusion. The BacterioScan system is a rapid diagnostic test that provides early information on urine culture results that could help to avoid overuse of empirical antimicrobials in patients with suspected UTI and decrease the workload of the Microbiology Laboratory.

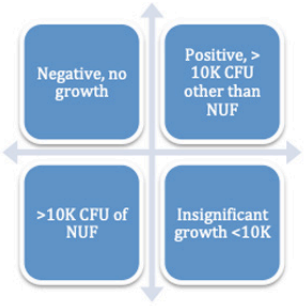

Figure1. Categories of Culture Results. Colony forming units (CFU) per ml. Normal Urogenital Flora (NUF)

Table 1.		BS – (%)	BS +(%)	UA – (%)	UA+ (%)	Comments
NEGATIVE CULTURE	No growth n=50	43 (86)	7 (14)	26 (52)	19 (38)	5 UA not completed
	Insignificant growth n=32	26 (81.2)	6 (18.7)	16 (50)	10 (31.2)	6 UA no WBC data
POSITIVE CULTURE	Colonization/ Overgrowth n=7	0 (0)	7 (100)	1 (14.3)	6 (85.7)	--
	Positive, growth n=31	4 (12.9)	27(87.1)	2 (6.5)	23 (74.2)	3 UA no|WBC data 3 UA not completed
PERFORMANCE	Sensitivity	89.5%		90.6%		
	Specificity	84.1%		59.1%		

BS: Bacterioscan; UA: Urinalysis; WBC: White Blood Cell Count

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

660. Extraction-Free 16S Ribosomal RNA (rRNA) Gene Amplification and Sequencing from Resected Cardiac Implantable Electronic Device (CIED) Sonicate Fluid

Zerelda Esquer Garrigos, MD[1]; Muhammad R. Sohail, MD[1]; Kerryl Greenwood-Quaintance, MS[2]; Scott A. Cunningham, MS, MT (ASCP) SM[2]; Prakhar Vijayvargiya, MBBS[2]; Robin Patel, MD[2]; Robin Patel, MD[2]; [1]Mayo Clinic College of Medicine, Rochester, Minnesota; [2]Mayo Clinic, Rochester, Minnesota

Session: 67. New Diagnostics

Thursday, October 3, 2019: 12:15 PM

Background. We recently demonstrated that 16S rRNA PCR/sequencing performed on biofilms dislodged from extracted CIEDs into a salt solution—referred to as "sonicate fluid' (SF)—may be used to detect pathogens in culture-negative CIED infection (*Clinical Infectious Diseases*, ciz266, doi:10.1093/cid/ciz266). The method we described included a DNA extraction/purification step, which can be time consuming and costly. Here, we evaluated an extraction-free approach to 16S rRNA gene PCR/sequencing.

Methods. 28 SF samples derived from explanted clinically-infected CIEDs were tested. Cases were categorized as "culture-positive" (C-P) if ≥20 cfu/10 mL were recovered, and as "culture-negative" (C-N), if <20 cfu/10 mL were detected in SF culture. The extraction-free method consisted of a single step of lysis at 1,000 rpm, 95°C for 5 minutes using an Eppendorf ThermoMixer®. DNA extraction (the comparator method) was performed using the ZymoBIOMICS™ Kit with modifications. Samples were processed using both methods, followed by amplification of the 16S rRNA gene and bi-directional Sanger sequencing. Crossing points (CPs) generated by the two approaches were compared. Organisms detected by the two PCR methods were compared with those detected with culture.

Results. Of the 28 samples tested, 13 were C-N and 15 C-P. The extraction-free method generated an amplicon in 13/15 C-P cases, with CPs ranging from 26 to 36 cycles *vs.* 100% (15/15) detected with the DNA extraction method and Cps of 19 to 32. Usable sequence length for the extraction-free method was of 359 (interquartile range, 307–390) *vs.* 390 (interquartile range, 308–396) base pairs with DNA extraction. Genus-level concordance between bacteria detected by culture in C-P samples and those found using the extraction-free and extraction methods was 92% (12/13) and 93% (14/15), respectively. Bacteria were detected by the extraction method in 2/13 C-N specimens, with none detected with an extraction-free method.

Conclusion. The described extraction-free method may be suitable for testing SF derived from CIEDs using 16S rRNA gene PCR/sequencing, saving time and cost. More studies are needed to establish clear cutoffs for interpretation of results and to assess for PCR inhibitors in the studied specimen-type.

Disclosures. Robin Patel, MD, ASM and IDSA: Other Financial or Material Support, Travel reimbursement, editor's stipends; CD Diagnostics, Merck, Hutchison Biofilm Medical Solutions, Accelerate Diagnostics, ContraFect, TenNor Therapeutics Limited, Shionogi: Grant/Research Support; Curetis, Specific Technologies, NextGen Diagnostics, PathoQuest, Qvella: Consultant; NBME, Up-to-Date, the Infectious Diseases Board Review Course: Honorarium recipient, Other Financial or Material Support; Patent on Bordetella pertussis/parapertussis PCR issued, a patent on a device/method for sonication with royalties paid by Samsung to Mayo Clinic, and a patent on an anti-biofilm substance issued: Other Financial or Material Support, Patents.

661. Ibalizumab Efficacy and Safety Through 48 Weeks of Treatment: Results of an Expanded Access Protocol (TMB-311)

Brinda Emu, MD[1]; Edwin DeJesus, MD[2]; Mezgebe Berhe, MD[3];
Jason Leider, MD, PhD[4]; Catherine Creticos, MD[5]; Steve Weinheimer, PhD[6];
Zvi Cohen, PhD[7]; [1]Yale University, New Haven, Connecticut; [2]Orlando Immunology Center, University of Central Florida College of Medicine, Orlando, Florida; [3]North Texas Infectious Diseases Consultants, Dallas, Texas; [4]Jacobi Medical Center, Bronx, New York; [5]Howard Brown Health, Chicago, Illinois; [6]TaiMed Biologics USA, Houston, Texas; [7]Theratechnologies Inc., Montreal, QC, Canada

Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Ibalizumab (IBA), a humanized monoclonal antibody, is the first CD4-directed post-attachment HIV-1 inhibitor. It was approved by the FDA in March 2018 based on results from the pivotal Phase 3 TMB-301 clinical study.

The TMB-311 expanded access protocol Cohort 2 enrolled treatment-experienced patients with multidrug-resistant (MDR) HIV-1 infection to further evaluate the efficacy, safety and tolerability of IBA in combination with an optimized background regimen (OBR). Here, we report the results through 48 weeks of treatment in these patients.

Methods. Major eligibility criteria included HIV-1 viral load (VL) >1000 copies/mL, resistance to ≥1 antiretroviral (ARV) medication from three different ARV classes and full viral sensitivity to ≥1 ARV agent. Treatment started with IBA 2000 mg intravenously (IV) on Day 0 and then 800 mg IV (maintenance) every 2 weeks thereafter. OBR with ≥1 fully active agent also started at Day 0.

Results. Cohort 2 enrolled 38 patients with a median age of 53 years, mostly male (87%) and white (53%). At Baseline, median VL was 4.7 $\log_{10}$ copies/mL, CD4 cell count was 26 cells/mm^3 and overall susceptibility score of 1. A ≥0.5 $\log_{10}$ decrease in VL from Baseline was achieved in 28 of 37 patients (76%) at Day 7. Of 24 patients who completed the Week 24 visit, 11 (46%) had HIV-1 RNA levels <50 copies/mL. Of 17 patients with a VL assessment at Week 48, 8 (47%) achieved <50 copies/mL. Seven patients did not have a Week 48 endpoint because they withdrew from the study to receive commercial IBA. At both time points, the median change in VL from Baseline was -2.6 $\log_{10}$ copies/mL. The most frequently reported treatment-emergent adverse events (TEAEs) were diarrhea (24%), headache (21%), and nausea, cough, rash, and fatigue (16% each). No injection site reactions related to IBA were reported. Most events were mild; 9 patients reported Grade ≥3 TEAEs. Two events were fatal (sepsis and cardiac arrest); neither related to IBA. One event of immune reconstitution inflammatory syndrome was reported and considered possibly related to IBA.

Conclusion. Results from Cohort 2 patients of TMB-311 (IBA + OBR) demonstrate durable viral suppression in this difficult-to-treat patient population and with a safety profile consistent with pivotal Phase 3 study of IBA.

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

662. Recurrence of Infection and Emergence of Drug Resistance After Treatment with Meropenem/Vaborbactam Compared with Ceftazidime/Avibactam in Carbapenem-Resistant *Enterobacteriaceae* Infections

Renee Ackley, PharmD, BCPS[1]; Danya Roshdy, PharmD, BCPS, BCIDP[2];
Jacqueline Isip, PharmD, BCPS, BCIDP[1];
Sarah B,. Minor, PharmD, BCPS-AQ ID[3];
Amanda L. Elchynski, Doctor of Pharmacy[4]; William E. Anderson, MS[1];
Gerald A. Capraro, PhD, D(ABMM)[1]; Christopher Polk, MD[1]; [1]Atrium Health, Charlotte, North Carolina; [2]Atrium Health - Antimicrobial Support Network, Charlotte, North Carolina; [3]AdventHealth, Winter Springs, Florida; [4]AdventHealth Orlando, Orlando, Florida

Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. Options for treatment of carbapenem-resistant *Enterobacteriaceae* (CRE) infections were historically limited to antibiotics with limited efficacy and significant toxicities. Ceftazidime/avibactam (CA) and meropenem/vaborbactam (MV) are superior to older regimens; however, a direct comparison of the agents is lacking. This study compared clinical outcomes including recurrence of infection and emergence of drug resistance in patients who received CA vs. MV for CRE infections.

Methods. This was a multicenter, retrospective cohort study of adults with CRE infections who received CA or MV for ≥72 hours from February 2015 to October 2018. Patients with localized urinary tract infection were excluded. The primary endpoint was clinical success (30-day survival, resolution of signs and symptoms of infection, sterilization of blood cultures within 7 days in patients with bacteremia, absence of recurrent infection). Secondary endpoints included 30- and 90-day mortality, adverse events (AE), recurrent CRE infection within 90 days, and development of resistance in patients with recurrent infection. We conducted a post hoc subgroup analysis in patients with recurrence to compare development of resistance in those who received CA monotherapy, CA combination therapy, and MV monotherapy.

Results. 131 patients were included (CA: 105 patients, MV: 26 patients), 40% had bacteremia. No statistical difference in clinical success was observed between groups (62% vs. 69%, respectively, $P = 0.49$). Patients in the CA arm received combination therapy more often than patients in the MV arm (61% vs. 15%, $P < 0.01$). No difference in 30- and 90-day mortality resulted among groups, but numerically higher rates of AE were observed in the CA group (38% vs. 23%, $P = 0.17$). In patients with recurrent infection, development of resistance occurred more often with CA monotherapy, though not statistically significant (Table 1). One case of MV resistance was observed in a patient who had received 4 prior courses of MV, but this episode was outside of the study period.

Conclusion. Clinical success was similar between the groups despite MV being used more often as monotherapy. Development of resistance and rates of AE were higher in the CA group compared with MV therapy.

Table 1. Post-hoc subgroup analysis of patients with recurrent CRE infection

n (%)	CA monotherapy n = 41	CA combination n = 64	MV monotherapy n = 22	P value
Recurrent CRE infection	9 (22.0)	6 (9.4)	3 (13.6)	0.20
MIC increase	5 (12.2)	1 (1.6)	0	0.13
Development of resistance	3 (7.3)	0	0	0.21

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

663. Efficacy and Safety of Lefamulin (LEF) vs. Moxifloxacin (MOX) for *Legionella pneumophila* (*LP*) in Patients with Community-Acquired Bacterial Pneumonia (CABP): Pooled Results From the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Phase 3 Clinical Trials

Andrew F. Shorr, MD, MPH, MBA[1]; Jennifer Schranz, MD[2];
Lisa Goldberg, MS[2]; Susanne Paukner, PhD[3]; Anita F. Das, PhD[4];
Gregory J. Moran, MD[5]; Christian Sandrock, MD[6];
Thomas M. File, Jr., MD[7]; Elizabeth Alexander, MD, MSc., FIDSA[2];
Steven P. Gelone, PharmD[2]; [1]Medstar Washington Hospital Center, Washington, DC; [2]Nabriva Therapeutics US, Inc., King of Prussia, Pennsylvania; [3]Nabriva Therapeutics GmbH, Vienna, Wien, Austria; [4]Das Consulting, Guerneville, California; [5]Olive View-UCLA Medical Center, Sylmar, California; [6]UC Davis School of Medicine, Sacramento, California; [7]Summa Health, Akron, Ohio

Session: 68. Novel Antimicrobials and Approaches Against Resistant Bugs
Thursday, October 3, 2019: 12:15 PM

Background. *LP* is associated with severe CABP, rapid onset, and high morbidity/mortality. Poor outcomes in CABP have been linked to receiving inappropriate empiric therapy or delayed treatment (tx). LEF, a novel IV/oral pleuromutilin, demonstrated efficacy/safety in noninferiority studies (LEAP 1/2) vs. MOX in adults with CABP. We report efficacy/safety of LEF in patients with *LP* based on a pooled analyses of LEAP 1/2 data.

Methods. In LEAP 1, PORT III–V patients received LEF 150 mg IV q12h for 5–7 days or MOX 400 mg IV q24h for 7 days, with optional IV-to-oral switch (600 mg LEF q12h or 400 mg MOX q24h). In LEAP 2, PORT II–IV patients received oral LEF for 5 days or oral MOX for 7 days. Both studies assessed early clinical response (ECR) at 96 ± 24 hours after first dose in the intent-to-treat (ITT; all randomized patients) population and investigator assessment of clinical response (IACR) at test-of-cure (TOC; 5–10 days after last dose) in the modified ITT (received ≥1 dose) and clinically evaluable (met predefined evaluability criteria) populations. *LP* was identified from baseline (BL) samples by culture, serology (IgG, Zeus *L. pneumophila* group 1–6 indirect fluorescent antibody assay), urine antigen testing (BinaxNOW), and real-time PCR (positive for *ssrA*). Efficacy analyses herein were done in the microbiological ITT (microITT, treated patients with BL CABP-causing pathogen), microITT-2 (no PCR), and microbiologically evaluable populations; safety analyses included all randomized/treated patients.

Results. Of 65 pooled microITT patients, median age was 60 y, 66% were male, 51% had a normal renal function, and 54%/25% were PORT III/IV. *LP* was identified in 9.3% (34/364) of LEF patients (7 [20.6%]/19 [55.9%]/8 [23.5%] PORT II/III/IV) and in 9.0% (31/345) of MOX patients (7 [22.6%]/16 [51.6%]/8 [25.8%] PORT II/III/IV), primarily by urine antigen or serology (table). Patients with *LP* in both tx groups achieved high and similar responses across all endpoints (Figures 1 and 2). In both tx groups, TEAE rates were low and comparable (~32%) and most were mild to moderate; 5 patients (3 LEF; 2 MOX) had treatment-emergent SAEs, all unrelated to tx. No patients died due to TEAEs; no LEF patients and 2 MOX patients discontinued tx due to TEAEs.