TABLE 1. Synergistic effect of subbactam, colistin, and fosfomycin sodium with biapenem against MDR A. baumanii (n = 40) by using the checkerboard assay

| Effect               | Subbactam + Biapenem | Colistin + Biapenem | Fosfomycin sodium with Biapenem |
|----------------------|-----------------------|---------------------|---------------------------------|
| Synergy (FIC<0.5)    | 30 (75)               | 40 (100)            | 33 (82.5)                       |
| Partial synergy (FIC<0.5) | 9 (20)           | 0                   | 7 (17.5)                        |
| Additive (FIC=1)     | 1 (5)                 | 0                   | 0                               |
| Indifference (FIC>1-4)| 0                    | 0                   | 0                               |
| Antagonism (FIC>4)   | 0                    | 0                   | 0                               |

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1535. Nitric Oxide-Releasing Chitosan for the Treatment of Multi-Drug Resistant Superbugs
Terry Kougooulos, PhD; Mark Schoentich, PhD; Pedro De Jesus Cruz, BS; Mona Aikonen, BS and Nathan Fisher, PhD; Lefko Charalambous, BS; Promila Pagadala, PhD; Ratu K Sharma-Kuinkel, PhD; Charles Girandemaro, M.R.; Blake Hedstrom, M.A.; A.A.; Laura Zitella Verbrick, PhD; Aaron Mccabe, PhD; Shivanand P. Lad, MD, PhD; Vance Fowler Jr., MD, MPH; and John R Perfect, MD, FIDSA, FIDSA

Background. Multi-drug resistant superbugs are a serious health threat due to limited treatment options and high mortality rates. Certain superbug strains are now resistant to as many as 36 representative FDA-approved antibiotics, including Colistin and Carbapenem antibiotics, widely considered as the last line of defense against untreatable infections. Nitric oxide (NO) is a diatomic free radical employed by the immune system to eradicate bacteria via oxidative and nitrosative stress. To facilitate storage and controlled release of NO, we have developed NO donor-modified biopolymers based on chitosan, a linear polysaccharide composed of randomly distributed β-linked-D-glucosamine and N-acetyl-D-glucosamine. Herein, we report the broad spectrum antibacterial action of low molecular weight (5 kDa) NO-releasing chitosan against Gram-positive and Gram-negative multi-drug-resistant bacterial species, including Klebsiella pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa.

Methods. MBC assays were performed using CLSI guidelines in a 96-well plate format. All assays were carried out in triplicate using a two-fold dilution range. The bacterial suspension was then diluted in assay medium to a target concentration of approximately 5 x 10^6 CFU/mL, after which it was added to all test and growth control wells, and allowed to incubate. Test wells were scored for the lowest NO concentration released from the chitosan to inhibit visual growth of the pathogen. After MIC determination, wells demonstrating inhibition were plated, incubated and resulting colonies counted to determine survival concentration. The lowest concentration of NO to inhibit ≥99.9% of a given test organism was reported as the MBC. Of note, chitosan alone does not exhibit any antibacterial action.

Results. MIC and MBC assays for NO-releasing chitosan against six multi-drug resistant strains are provided below.

Conclusion. The properties of the NO-releasing chitosan, including water solubility, make it an excellent drug candidate for treating respiratory infections. Such development is currently underway.

Disclosures. All authors: No reported disclosures.

1536. Discovery of Antifungal Compounds from Kampo Medicine Against Dermatophytes
Xia Da, Doctoral candidate; Department of Dermatology, Shimane University Faculty of Medicine, Izumo, Japan

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Background. Kampo medicine mainly contain crude extracts of natural products such as plants, animals, and minerals that are prepared according to classical Kampo methodologies. Since plants synthesize numerous antimicrobial components such as plant defensins, Kampo medicine likely contain potent antimicrobial constituents. We have tested antifungal activity of 61 commercially available Kampo medicines by using micro-broth dilution assay with Trichophyton rubrum (T. rubrum), and found that 7 of them had antifungal activity. Among these 7 Kampo medicines 6 contained Ou-gon which derived from the roots of Scutellaria baicalensis Georgi, and a crude extract of Ou-gon exhibited significant antifungal activity. This study aims to identify antifungal components contained in Ou-gon, and determine their antifungal mechanisms.

Methods. T. rubrum, T. mentagrophytes, Aspergillus fumigatus (A. fumigatus) and Candida albicans (C. albicans) were used for antifungal activity assay. The antifungal activity assay was performed by measuring 595 nm absorbance in micro-broth dilution assay. Antifungal components were analyzed by high performance liquid chromatography (HPLC), and identified by liquid chromatography electrospray ionisation mass spectrometry (LC-ESI-MS/MS). TUNEL assay, SYTOX-Green Uptake analyses, intracellular reactive oxygen species accumulation assay, mitochondrial membrane potential assay, scanning electron microscopy; and transmission electron microscopy were used to clarify the antifungal mechanism of active components.

Results. Upon HPLC analysis, two low molecular weight-compounds were isolated having potent antifungal activity. The two compounds were identified as Baicalein and Wogonin by LC-ESI-MS/MS. Baicalein showed antifungal activity for T. rubrum, T. mentagrophytes, A. fumigatus and C. albicans. Wogonin showed antifungal activity for all except C. albicans. Detection of antifungal mechanism of Baicalein and Wogonin suggested that their mode of action is apoptosis-like programmed cell death.

Conclusion. Baicalein and Wogonin are major compounds to have antifungal activity in Kampo medicine. This study may contribute to the development of new and safe antifungal drugs, especially for the clinical treatment of pathogenic fungal infections.

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1537. Feasibility of Neurapheresis as a Therapy for Multidrug Resistant Gram-negative Bacterial Meningitis
Velpa Ballard, BS; Bilal Ashraf, BS; Tiffany Eijerene, BS; Brenda Hansen, MS; Lefko Charalambous, BS; Promila Pagadala, PhD; Ratu K Sharma-Kuinkel, PhD; Charles Girandemaro, M.R.; Blake Hedstrom, M.A.; A.A.; Laura Zitella Verbrick, PhD; Aaron Mccabe, PhD; Shivanand P. Lad, MD, PhD; Vance Fowler Jr., MD, MPH; and John R Perfect, MD, FIDSA, FIDSA

Background. The World Health Organization has identified Pseudomonas, Acinetobacter and Klebsiella (PAK) as three multidrug resistant (MDR) gram-negative pathogens that pose a threat to human health. The greatest threat lies in hospitals, nursing homes, and patients with devices such as intravenous catheters and ventilators. Gram-negative bacterial meningitis (GBM) manifests when these bacteria invade the central nervous system. Due to the threat of increasing antibiotic resistance and the high mortality associated with MDR GBM, we have tested a closed-loop, extracorporeal cerebrospinal fluid (CSF) filtration system (Neurapheresis®) for its applicability in this context. Here we demonstrate feasibility of Neurapheresis for MDR GBM and characterize system parameters for bacterial clearance.

Methods. PAK cultures were grown and diluted to 1 x 10^6 cells/mL in artificial CSF or Luria-Miller broth. Both single pass and closed loop filtration were performed with various tangential flow filtration (TFF) and dead-end filter paradigms. Samples were taken either immediately post-filter or after every full CSF volume cycle (150 mL) during a long term closed loop experiment. Bacterial load, endotoxin and cytokines were quantified.

Results. In single pass tests, 5kDa and 100kDa TFF filters and 0.2μm and 0.45μm dead-end filters excluded all PAK bacteria completely. The 100kDa and 5kDa TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL1). In closed-loop experiments, both TFF filters demonstrated a 1–2 Log CFU (90–99%) reduction of all PAK organisms over 4 filtration cycles.

Conclusion. Neurapheresis shows potential to be an efficient multi-modal tool for controlling and treating MDR GBM in this in vitro model. Extending closed loop filtration over time demonstrates the capability for rapid sterilization of the CSF. Future iterations may include adjunctive intrathecal drug delivery to further accelerate elimination of bacteria. Reduction of both endotoxin and cytokines by Neurapheresis may have significant implications for controlling the damaging neuro-inflammatory response during MDR GBM.

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515. Evaluation of a 15-valent Pneumovac Conjugate Vaccine in an Adult Rhesus Macaque Immunogenicity Model

Jinnie Jie, MS; Robin Kauthold, MS; Debra Mccuinness, MS; Yuhua Zhang, MS; William Smith, PhD; Cecilia Guavarelli, MS; Michael Winters, PhD; Ludy Musey, PhD; Michael Kossinski, PhD and Julie Skinner, PhD; Merck & Co. Inc., West Point, Pennsylvania

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Background. Streptococcus pneumoniae (pneumococcus) is a leading cause of a variety of diseases, including bacteremia, meningitis, and pneumonia, among older adults in the United States. Immunization with pneumovac vaccines is an effective way to prevent these diseases. In this study, we evaluated the immunogenicity of a 15-valent pneumovac conjugate vaccine (PCV15) in adult rhesus macaques.

Methods. Animals were intramuscularly immunized with PNEUMOVAX 23 and PCV15 vaccine (5 animals/group) and sera were collected before immunization and 30, 60, and 90 days after the immunization. Sera were assessed using multiplexed electrochemiluminescent (ECL) assays to measure serotype-specific IgG antibodies to all vaccine serotypes and multiplexed opsonophagocytic killing assays (MOPA) to measure functional antibody responses to 15 vaccine serotypes.

Results. At day 30 post immunization, 16 out of the 23 serotypes in PNEUMOVAX 23 groups induced statistically significant higher ECL titers compared with pre bleed, ranging from 1.6-fold (19A) to 28.3-fold (15B). Compared with PNEUMOVAX 23, PCV15 induced much higher ECL titers. Thirteen out of the 15 serotypes in PCV15 groups induced statistically significant higher ECL titers compared with pre bleed, ranging from 7.4-fold (14) to 47.3-fold (4). The ECL antibody titers gradually decreased from day 30 to day 90 for both groups. We also compared the functional MOPA titers of the day 30 sera compared with pre bleed for 15 vaccine serotypes. Out of the 14 common serotypes in the PCV15 vaccine, the PCV23 vaccinated macaques had a >4-fold increase in MOPA titer, ranging from 4-fold (22F) to 3902-fold (3F) and 11 serotypes in the PCV15 vaccinated macaques had a >4-fold increase in MOPA titer, ranging from 6.3-fold (23F) to 4445-fold (7F). Twelve out of the 14 common serotypes in the PCV15 immunization group had a >4-fold increase in MOPA titer compared with the PNEUMOVAX 23 group, although they didn't reach statistical significance due to high variability.

Conclusion. These data demonstrate that a single dose of PCV15 is highly immunogenic in adult rhesus macaques and has better immunogenicity for most common serotypes compared with PNEUMOVAX 23. However, PNEUMOVAX 23 offers broader serotype coverage with 9 additional serotypes contained in the vaccine.

Disclosures.

J. Xie, Merck & Co. Inc: Employee, Salary; R. Kauthold, Merck & Co. Inc: Employee, Salary; D. Mccuinness, Merck & Co. Inc: Employee, Salary; Y. Zhang, Merck & Co. Inc: Employee, Salary; W. Smith, Merck & Co. Inc: Employee, Salary; C. Giovarelli, Merck & Co. Inc: Employee, Salary; M. Winters, Merck & Co. Inc: Employee, Salary; L. Musey, Merck & Co. Inc: Employee, Salary; M. Kossinski, Merck & Co. Inc: Employee, Salary; J. Skinner, Merck & Co. Inc: Employee, Salary

1539. Foley Catheter with Peri-Urethral Antimicrobial Irrigation for the Prevention of Catheter Associated Urinary Tract Infections – Assessment in an In Vitro Model

Joel Rosenblatt, PhD; Ruth Reitzel, MS; Nyle Vargas-Cruz, BS; Anne-Marie Chaffart, MD; Ray Y. Hachem, MD and Issam Raad, MD; 1515 Holcombe – Suite FCT2.6303, UT MD Anderson Cancer Center, Houston, Texas, 2Infectious Diseases, Infection Control & Employee Health, University of Texas MD Anderson Cancer Center, Houston, Texas, 3UT MD Anderson Cancer Center, Houston, Texas, 4University of Texas MD Anderson Cancer Center, Houston, Texas, 5Department of Infectious Diseases, Infection Control and Employee Health, The University of Texas MD Anderson Cancer Center, Houston, Texas

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Background. Catheter associated urinary tract infections (CAUTIs) are a significant clinical issue with substantial morbidity and costs. CAUTIs are primarily caused by colonization of the external surface of Foley catheter which serve as conduits for colonization of microorganisms to access the bladder. In order to prevent these CAUTIs, we developed a double-cuff Foley catheter with a novel irrigation cuff for daily irrigation of the perirethral space with a biocompatible antimicrobial disinfecting solution. This study assessed the efficacy of this system for reducing external surface microbial colonization of catheters in an in vitro model.

Methods. The novel double cuff Foley and disinfectant solutions were evaluated in an established in vitro CAUTI model (Gaonkar, et al 2003) where a Foley catheter indwelled in a simulated urethra. 5 × 10⁴ CFU of common uropathogens (MRSA, E. coli, C. albicans) were allowed to attach to the external catheter surface at mean end of the catheter for 2 hours at 37°C. Subsequently, 3 mL of disinfectant solutions were instilled through the irrigation cuff and covered the perirethral catheter surfaces. Catheters were then incubated an additional 24–48 hours at 37°C, removed, cut into segments, and adherent organisms were quantified by sonication. Disinfectant solutions evaluated included various combinations of 1% polygalacturonic acid (PG), 0.4% caprylic acid (CAP) and (dilute) 0.3% H₂O₂.

Results. For all organisms tested only the triple combination periurethral flush (PG-CAP+H₂O₂) completely prevented biofilm colonization of catheters indicating antimicrobial synergy of the component agents. Control catheters grew >10⁵ CFU/segment. Single agent or double agents combinations were only partially effective in preventing colonization by all three pathogens.

Conclusion. The PG + CAP + H₂O₂ periurethral disinfectant flush instilled through an irrigation cuff in a novel double-cuff Foley catheter was able to completely prevent microbial colonization of the external catheter surface by MRSA, E. coli and C. albicans in an in vitro CAUTI model. In vivo studies are needed to further evaluate this system for prevention of CAUTI.

Disclosures. J. Rosenblatt, Infective Technologies, LLC: Co-Inventor of the Nitroglycerin-Citrate-Ethanol catheter lock solution technology which is owned by the University of Texas MD Anderson Cancer Center (UTMDACC) and has been licensed by Novel Anti-Infective Technologies, LLC in which Dr. Rosenblatt is a shareholder, Licensing agreement or royalty; UT MD Anderson Cancer Center: Co-Inventor of the Nitroglycerin-Citrate-Ethanol catheter lock solution technology which is owned by the University of Texas MD Anderson Cancer Center (UTMDACC) and has been licensed by Novel Anti-Infective Technologies, LLC in which Dr. Rosenblatt is a s and Shareholder, Licensing agreement or royalty; J. Raad, Merck: Grant Investigator, Research grant; Allergan: Grant Investigator, Research grant; Infective Technologies, LLC: Co-Inventor of the Nitroglycerin-Citrate-Ethanol catheter lock solution technology which is owned by the University of Texas MD Anderson Cancer Center (UTMDACC) and has been licensed by Novel Anti-Infective Technologies, LLC in which Dr. Raad is a s and Shareholder, Licensing agreement or royalty