SESSION 363 - Literature Review

Itinerary

June 10, 2018, 8:45 AM - 10:45 AM	Sydney Marcus Auditorium, Building A, Level 4 and ASM Microbe at Play, Building B, Lobby

DESCRIPTION

This session reviews the top papers in clinical and public health microbiology and infectious diseases. The top papers in Gram negative infections, Gram positive infections, transplant infectious diseases, vaccines, and HIV and diagnostics will be presented in rapid-fire format.

Upon completion of this Plenary, the participant should be able to:

Review the most impactful papers in infectious diseases and clinical microbiology in 2018.

Discuss emerging challenges and current literature on the management of Gram positive and Gram negative infections.

Discuss current trends in transplant infectious diseases, vaccines and HIV.

Track

CIV01 - Clinical Studies of Adult Infectious Diseases AAR01 - Surveillance of Antibacterial Resistance CIV06 - Vaccines and Immunization Science CPHM12 - Molecular Diagnostic Microbiology

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Curated Itineraries

Bench Technologists

7 Presentations

8:45 AM - 10:45 AM	1 - **Moderator** **Romney Humphries**; Accelerate Diagnostics, Tucson, AZ	Itinerary
8:45 AM - 9:05 AM	2 - **Gram Negative Infections** **Pranita Tamma**; John Hopkins, Baltimore, MD	Itinerary
9:05 AM - 9:25 AM	3 - **Gram Positive Bacterial Infections** **Cesar Arias**; Univ. of Texas Med. Sch. at Houston, Houston, TX	Itinerary
9:25 AM - 9:45 AM	4 - **Transplant Infectious Diseases** **Aric Gregson**; AG Infectious Disease, Los Angeles, CA	Itinerary
9:45 AM - 10:05 AM	5 - **HIV** **Jose Gatell**; Univ. de Barcelona, Barcelona, Spain	Itinerary
10:25 AM - 10:45 AM	6 - **Infectious Diseases Diagnostics** **Lars Westblade**; Cornell Univ., New York, NY	Itinerary
10:25 AM - 10:45 AM	- **Q/A** **x. x**; x, Atlanta, GA	Itinerary

http://www.abstractsonline.com/pp8/#!/4623/session/1189

8:45 AM - 9:05 AM 2 - **Gram Negative Infections**

Pranita Tamma; John Hopkins, Baltimore, MD

1. Bevan, E.R., A.M. Jones, and P.M. Hawkey, Global epidemiology of CTX-M beta-lactamases: temporal and geographical shifts in genotype. *J Antimicrob Chemother*, 2017. **72**(8): p. 2145-2155.
Globally, rates of ESBL-producing Enterobacteriaceae are rising. We undertook a literature review, and present the temporal trends in blaCTX-M epidemiology, showing that blaCTX-M-15 and blaCTX-M-14 have displaced other genotypes in many parts of the world. Explanations for these changes can be attributed to: (i) horizontal gene transfer (HGT) of plasmids; (ii) successful Escherichia coli clones; (iii) ESBLs in food animals; (iv) the natural environment; and (v) human migration and access to basic sanitation. We also provide explanations for the changing epidemiology of blaCTX-M-2 and blaCTX-M-27. Modifiable anthropogenic factors, such as poor access to basic sanitary facilities, encourage the spread of blaCTX-M and other antimicrobial resistance (AMR) genes, such as blaNDM, blaKPC and *mcr-1*. We provide further justification for novel preventative and interventional strategies to reduce transmission of these AMR genes.

2. Falagas, M.E., et al., Activity of cefiderocol (S-649266) against carbapenem-resistant Gram-negative bacteria collected from inpatients in Greek hospitals. *J Antimicrob Chemother*, 2017. **72**(6): p. 1704-1708.
Background: Cefiderocol (S-649266), a siderophore cephalosporin, utilizes a novel mechanism of entry into the periplasmic space of Gram-negative bacteria and is broadly stable to ESBLs and carbapenemases. Methods: A collection of carbapenem-resistant Gram-negative bacteria isolated from clinical specimens in 18 Greek hospitals was tested for susceptibility to cefiderocol, meropenem, ceftazidime, cefepime, ceftazidime/avibactam, ceftolozane/tazobactam, aztreonam, amikacin, ciprofloxacin, colistin and tigecycline. Broth microdilution plates were used to determine MICs. Results: In total 189 non-fermentative Gram-negative bacteria (107 *Acinetobacter baumannii* and 82 *Pseudomonas aeruginosa*) and 282 Enterobacteriaceae (including 244 *Klebsiella pneumoniae*, 14 *Enterobacter cloacae* and 11 *Providencia stuartii*) were studied. For both *A. baumannii* and *P. aeruginosa* the MIC 90 of cefiderocol was 0.5 mg/L. For *K. pneumoniae*, *E. cloacae* and *P. stuartii* the MIC 90 of cefiderocol was 1, 1 and 0.5 mg/L, respectively. Tigecycline was the second most active antibiotic, followed by colistin. Conclusions: Cefiderocol exhibited greater antimicrobial activity in vitro against carbapenem-resistant Gram-negative bacteria than comparator antibiotics.

3. Gu, D., et al., A fatal outbreak of ST11 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* in a Chinese hospital: a molecular epidemiological study. *Lancet Infect Dis*, 2018. **18**(1): p. 37-46.
BACKGROUND: Hypervirulent *Klebsiella pneumoniae* strains often cause life-threatening community-acquired infections in young and healthy hosts, but are usually sensitive to antibiotics. In this study, we investigated a fatal outbreak of ventilator-associated pneumonia caused by a new emerging hypervirulent *K pneumoniae* strain. METHODS: The outbreak occurred in the integrated intensive care unit of a new branch of the Second Affiliated Hospital of Zhejiang University (Hangzhou, China). We collected 21 carbapenem-resistant *K pneumoniae* strains from five patients and characterised these strains for their antimicrobial susceptibility, multilocus sequence types, and genetic relatedness using VITEK-2 compact system, multilocus sequence typing, and whole genome sequencing. We selected one representative isolate from each patient to establish the virulence potential using a human neutrophil assay and *Galleria mellonella* model and to establish the genetic basis of their hypervirulence phenotype. FINDINGS: All five patients had undergone surgery for multiple trauma and subsequently received mechanical ventilation. The patients were aged 53-73 years and were admitted to the intensive care unit between late February and April, 2016. They all had severe pneumonia, carbapenem-resistant *K pneumoniae* infections, and poor responses to antibiotic treatment and died due to severe lung infection, multiorgan failure, or septic shock. All five representative carbapenem-resistant *K pneumoniae* strains belonged to the ST11 type, which is the most prevalent carbapenem-resistant *K pneumoniae* type in China, and originated from the same clone. The strains were positive on the string test, had survival of about 80% after 1 h incubation in human neutrophils, and killed 100% of wax moth larvae (*G mellonella*) inoculated with 1 x 10(6) colony-forming units of the specimens within 24 h, suggesting that they were hypervirulent *K pneumoniae*. Genomic analyses showed that the emergence of these ST11 carbapenem-resistant hypervirulent *K pneumoniae* strains was due to the acquisition of a roughly 170 kbp pLVPK-like virulence plasmid by classic ST11 carbapenem-resistant *K pneumoniae* strains. We also detected these strains in specimens collected in other regions of China. INTERPRETATION: The ST11 carbapenem-resistant hypervirulent *K pneumoniae* strains pose a substantial threat to human health because they are simultaneously hypervirulent, multidrug resistant, and highly transmissible. Control measures should be implemented to prevent further dissemination of such organisms in the hospital setting and the community. FUNDING: Chinese National Key Basic Research and Development Program and Collaborative Research Fund of Hong Kong Research Grant Council.

4. Haidar, G., et al., Ceftolozane-Tazobactam for the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Infections: Clinical Effectiveness and Evolution of Resistance. *Clin Infect Dis*, 2017. 65(1): p. 110-120.
Background: Data on the use of ceftolozane-tazobactam and emergence of ceftolozane-tazobactam resistance during multidrug resistant (MDR)-*Pseudomonas aeruginosa* infections are limited. Methods: We performed a retrospective study of 21 patients treated with ceftolozane-tazobactam for MDR-*P. aeruginosa* infections. Whole genome sequencing and quantitative real-time polymerase chain reaction were performed on longitudinal isolates. Results: Median age was 58 years; 9 patients (43%) were transplant recipients. Median simplified acute physiology score-II (SAPS-II) was 26. Eighteen (86%) patients were treated for respiratory tract infections; others were treated for bloodstream, complicated intraabdominal infections, or complicated urinary tract infections. Ceftolozane-tazobactam was discontinued in 1 patient (rash). Thirty-day all-cause and attributable mortality rates were 10% (2/21) and 5% (1/21),

respectively; corresponding 90-day mortality rates were 48% (10/21) and 19% (4/21). The ceftolozane-tazobactam failure rate was 29% (6/21). SAPS-II score was the sole predictor of failure. Ceftolozane-tazobactam resistance emerged in 3 (14%) patients. Resistance was associated with *de novo* mutations, rather than acquisition of resistant nosocomial isolates. *ampC* overexpression and mutations were identified as potential resistance determinants. Conclusions: In this small study, ceftolozane-tazobactam was successful in treating 71% of patients with MDR-*P. aeruginosa* infections, most of whom had pneumonia. The emergence of ceftolozane-tazobactam resistance in 3 patients is worrisome and may be mediated in part by *AmpC*-related mechanisms. More research on treatment responses and resistance during various types of MDR-*P. aeruginosa* infections is needed to define ceftolozane-tazobactam's place in the armamentarium.

5. Harris PN & Paterson D. The MERINO Trial: Piperacillin-tazobactam versus meropenem for bloodstream infections caused by third-generation cephalosporin non-susceptible *Escherichia coli* or *Klebsiella* spp.: an international randomised trial. *In press.*
No abstract available.

6. Paul, M., et al., Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis*, 2018. **18**(4): p. 391-400.
BACKGROUND: Colistin-carbapenem combinations are synergistic in vitro against carbapenem-resistant Gram-negative bacteria. We aimed to test whether combination therapy improves clinical outcomes for adults with infections caused by carbapenem-resistant or carbapenemase-producing Gram-negative bacteria. METHODS: A randomised controlled superiority trial was done in six hospitals in Israel, Greece, and Italy. We included adults with bacteraemia, ventilator-associated pneumonia, hospital-acquired pneumonia, or urosepsis caused by carbapenem-non-susceptible Gram-negative bacteria. Patients were randomly assigned (1:1) centrally, by computer-generated permuted blocks stratified by centre, to intravenous colistin (9-million unit loading dose, followed by 4.5 million units twice per day) or colistin with meropenem (2-g prolonged infusion three times per day). The trial was open-label, with blinded outcome assessment. Treatment success was defined as survival, haemodynamic stability, improved or stable Sequential Organ Failure Assessment score, stable or improved ratio of partial pressure of arterial oxygen to fraction of expired oxygen for patients with pneumonia, and microbiological cure for patients with bacteraemia. The primary outcome was clinical failure, defined as not meeting all success criteria by intention-to-treat analysis, at 14 days after randomisation. This trial is registered at ClinicalTrials.gov, number NCT01732250, and is closed to accrual. FINDINGS: Between Oct 1, 2013, and Dec 31, 2016, we randomly assigned 406 patients to the two treatment groups. Most patients had pneumonia or bacteraemia (355/406, 87%), and most infections were caused by Acinetobacter baumannii (312/406, 77%). No significant difference between colistin monotherapy (156/198, 79%) and combination therapy (152/208, 73%) was observed for clinical failure at 14 days after randomisation (risk difference -5.7%, 95% CI -13.9 to 2.4; risk ratio [RR] 0.93, 95% CI 0.83-1.03). Results were similar among patients with A baumannii infections (RR 0.97, 95% CI 0.87-1.09). Combination therapy increased the incidence of diarrhoea (56 [27%] vs 32 [16%] patients) and decreased the incidence of mild renal failure (37 [30%] of 124 vs 25 [20%] of 125 patients at risk of or with kidney injury). INTERPRETATION: Combination therapy was not superior to monotherapy. The addition of meropenem to colistin did not improve clinical failure in severe A baumannii infections. The trial was unpowered to specifically address other bacteria. FUNDING: EU AIDA grant Health-F3-2011-278348.

7. Shelburne, S.A., et al., Whole-Genome Sequencing Accurately Identifies Resistance to Extended-Spectrum β-Lactams for Major Gram-Negative Bacterial Pathogens. *Clin Infect Dis*, 2017. **65**(5): p. 738-745.
Background: There is marked interest in using DNA-based methods to detect antimicrobial resistance (AMR), with targeted polymerase chain reaction (PCR) approaches increasingly being incorporated into clinical care. Whole-genome sequencing (WGS) could offer significant advantages over targeted PCR for AMR detection, particularly for species where mutations are major drivers of AMR. Methods: Illumina MiSeq WGS and broth microdilution (BMD) assays were performed on 90 bloodstream isolates of the 4 most common gram-negative bacteria causing bloodstream infections in neutropenic patients. The WGS data, including both gene presence/absence and detection of mutations in an array of AMR-relevant genes, were used to predict resistance to 4 beta-lactams commonly used in the empiric treatment of neutropenic fever. The genotypic predictions were then compared to phenotypic resistance as determined by BMD and by commercial methods during routine patient care. Results: Of 133 putative instances of resistance to the beta-lactams of interest identified by WGS, only 87 (65%) would have been detected by a typical PCR-based approach. The sensitivity, specificity, and positive and negative predictive values for WGS in predicting AMR were 0.87, 0.98, 0.97, and 0.91, respectively. Using BMD as the gold standard, our genotypic resistance prediction approach had a significantly higher positive predictive value compared to minimum inhibitory concentrations generated by commercial methods (0.97 vs 0.92; P = .025). Conclusions: These data demonstrate the potential feasibility of using WGS to guide antibiotic treatment decisions for patients with life-threatening infections for an array of medically important pathogens.

8. Zhong, L.L., et al., High Rates of Human Fecal Carriage of *mcr-1*-Positive Multidrug-Resistant Enterobacteriaceae Emerge in China in Association with Successful Plasmid Families. *Clin Infect Dis,* 2018. **66**(5): p. 676-685.
Background: *mcr-1*-mediated colistin resistance in Enterobacteriaceae is concerning, as colistin is used in treating multidrug-resistant Enterobacteriaceae infections. We identified trends in human fecal *mcr-1*-positivity rates and colonization with *mcr-1*-positive, third-generation cephalosporin-resistant (3GC-R) Enterobacteriaceae in Guangzhou, China, and investigated the genetic contexts of *mcr-1* in *mcr-1*-positive 3GC-R strains. Methods: Fecal samples were collected from in-/out-patients submitting specimens to 3 hospitals (2011-

2016). *mcr-1* carriage trends were assessed using iterative sequential regression. A subset of *mcr-1*-positive isolates was sequenced (whole-genome sequencing [WGS], Illumina), and genetic contexts (flanking regions, plasmids) of *mcr-1* were characterized. Results: Of 8022 fecal samples collected, 497 (6.2%) were *mcr-1* positive, and 182 (2.3%) harbored *mcr-1*-positive 3GC-R Enterobacteriaceae. We observed marked increases in *mcr-1* (0% [April 2011] to 31% [March 2016]) and more recent (since January 2014; 0% [April 2011] to 15% [March 2016]) increases in human colonization with *mcr-1*-positive 3GC-R Enterobacteriaceae ($P < .001$). *mcr-1*-positive 3GC-R isolates were commonly multidrug resistant. WGS of *mcr-1*-positive 3GC-R isolates (70 *Escherichia coli*, 3 *Klebsiella pneumoniae*) demonstrated bacterial strain diversity; *mcr-1* in association with common plasmid backbones (IncI, IncHI2/HI2A, IncX4) and sometimes in multiple plasmids; frequent *mcr-1* chromosomal integration; and high mobility of the *mcr-1*-associated insertion sequence ISApl1. Sequence data were consistent with plasmid spread among animal/human reservoirs. Conclusions: The high prevalence of *mcr-1* in multidrug-resistant *E. coli* colonizing humans is a clinical threat; diverse genetic mechanisms (strains/plasmids/insertion sequences) have contributed to the dissemination of *mcr-1*, and will facilitate its persistence.

9:05 AM - 9:25 AM **3 - Gram Positive Bacterial Infections**

Cesar Arias; Univ. of Texas Med. Sch. at Houston, Houston, TX

1. Bhardwaj, P., et al., Reduced Chlorhexidine and Daptomycin Susceptibility in Vancomycin-Resistant Enterococcus faecium after Serial Chlorhexidine Exposure. *Antimicrob Agents Chemother*, 2018. **62**(1).
Vancomycin-resistant Enterococcus faecium strains (VREfm) are critical public health concerns because they are among the leading causes of hospital-acquired bloodstream infections. Chlorhexidine (CHX) is a bisbiguanide cationic antiseptic that is routinely used for patient bathing and other infection control practices. VREfm are likely frequently exposed to CHX; however, the long-term effects of CHX exposure have not been studied in enterococci. In this study, we serially exposed VREfm to increasing concentrations of CHX for a period of 21 days in two independent experimental evolution trials. Reduced CHX susceptibility emerged (4-fold shift in CHX MIC). Subpopulations with reduced daptomycin (DAP) susceptibility were detected, which were further analyzed by genome sequencing and lipidomic analysis. Across the trials, we identified adaptive changes in genes with predicted or experimentally confirmed roles in chlorhexidine susceptibility (efrE), global nutritional stress response (relA), nucleotide metabolism (cmk), phosphate acquisition (phoU), and glycolipid biosynthesis (bgsB), among others. Moreover, significant alterations in membrane phospholipids were identified for some populations with reduced DAP susceptibility. Our results are clinically significant because they identify a link between serial subinhibitory CHX exposure and reduced DAP susceptibility. In addition, the CHX-induced genetic and lipidomic changes described in this study offer new insights into the mechanisms underlying the emergence of antibiotic resistance in VREfm.

2. Chia, J.H., et al., *Clostridium innocuum* is a vancomycin-resistant pathogen that may cause antibiotic-associated diarrhoea. *Clin Microbiol Infect*, 2018.
OBJECTIVES: *Clostridiuminnocuum* can cause extraintestinal infection in patients with underlying diseases. The role of *C. innocuum* in antibiotic-associated diarrhoea (AAD) remains unknown. METHODS: Clinical information of 103 patients from whom *C. innocuum* was isolated was reviewed. We carried out cellular and animal experiments to examine the pathogenic potential of *C. innocuum* in AAD. RESULTS: Eighty-eight per cent (91/103) of the 103 patients received antibiotics within 2 weeks of diarrhoea onset. Patients were further classified into two groups, severe colitis and diarrhoea, according to clinical severity level. The mortality rate was 13.6% (14/103) among the patients from whom *C. innocuum* was isolated. The lowest concentrations at which 90% of the isolates were inhibited for metronidazole and vancomycin were 0.5 and 16 mg/L, respectively. All isolates tested were susceptible to metronidazole but resistant to vancomycin. Nineteen randomly selected isolates (ten from severe colitis group, nine from diarrhoea group) were subjected to further in vitro cellular examinations. The level of cytotoxicity to Vero cells was significantly higher in isolates from the severe colitis group at both 24 and 48 hours after inoculation (24 and 48 hours, p 0.042 and 0.033, respectively). We observed apoptotic changes that subsequently led to cell death in *C. innocuum*-infected Vero cells. Tissue damages, necrotic changes and oedema were observed in the mouse ileal loop infected by *C. innocuum*. CONCLUSIONS: Vancomycin-resistant *C. innocuum* may play a potential role as a causative agent of AAD. The clinical manifestations of AAD caused by *C. innocuum* were diarrhoea or severe colitis, including pseudomembranous colitis.

3. Collins, J., et al., Dietary trehalose enhances virulence of epidemic *Clostridium difficile*. *Nature*, 2018. **553**(7688): p. 291-294.
Clostridium difficile disease has recently increased to become a dominant nosocomial pathogen in North America and Europe, although little is known about what has driven this emergence. Here we show that two epidemic ribotypes (RT027 and RT078) have acquired unique mechanisms to metabolize low concentrations of the disaccharide trehalose. RT027 strains contain a single point mutation in the trehalose repressor that increases the sensitivity of this ribotype to trehalose by more than 500-fold. Furthermore, dietary trehalose increases the virulence of a RT027 strain in a mouse model of infection. RT078 strains acquired a cluster of four genes involved in trehalose metabolism, including a PTS permease that is both necessary and sufficient for growth on low concentrations of trehalose. We propose that the implementation of trehalose as a food additive into the human diet, shortly before the emergence of these two epidemic lineages, helped select for their emergence and contributed to hypervirulence.

4. Fenton, A.K., et al., Phosphorylation-dependent activation of the cell wall synthase PBP2a in Streptococcus pneumoniae by MacP. *Proc Natl Acad Sci U S A*, 2018. **115**(11): p. 2812-2817.
Most bacterial cells are surrounded by an essential cell wall composed of the net-like heteropolymer peptidoglycan (PG). Growth and division of bacteria are intimately linked to the expansion of the PG meshwork and the construction of a cell wall septum that separates the nascent daughter cells. Class A penicillin-binding proteins (aPBPs) are a major family of PG synthases that build the wall matrix. Given their central role in cell wall assembly and importance as drug targets, surprisingly little is known about how the activity of aPBPs is controlled to properly coordinate cell growth and division. Here, we report the identification of MacP (SPD_0876) as a membrane-anchored cofactor of PBP2a, an aPBP synthase of the Gram-positive pathogen *Streptococcus pneumoniae* We show that MacP localizes to the division site of *S. pneumoniae*, forms a complex with PBP2a, and is required for the in vivo activity of the synthase. Importantly, MacP was also found to be a substrate for the kinase StkP, a global cell cycle regulator. Although StkP has been implicated in controlling the balance between the elongation and septation modes of cell wall synthesis, none of its substrates are known to modulate PG synthetic activity. Here we show that a phosphoablative substitution in MacP that blocks StkP-mediated phosphorylation prevents PBP2a activity without affecting the MacP-PBP2a interaction. Our results thus reveal a direct connection between PG synthase function and the control of cell morphogenesis by the StkP regulatory network.

5. Kao, D., et al., Effect of Oral Capsule- vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection: A Randomized Clinical Trial. *JAMA*, 2017. **318**(20): p. 1985-1993.
Importance: Fecal microbiota transplantation (FMT) is effective in preventing recurrent *Clostridium difficile* infection (RCDI). However, it is not known whether clinical efficacy differs by route of delivery. Objective: To determine whether FMT by oral capsule is noninferior to colonoscopy delivery in efficacy. Design, Setting, and Participants: Noninferiority, unblinded, randomized trial conducted in 3 academic centers in Alberta, Canada. A total of 116 adult patients with RCDI were enrolled between October 2014 and September 2016, with follow-up to December 2016. The noninferiority margin was 15%. Interventions: Participants were randomly assigned to FMT by capsule or by colonoscopy at a 1:1 ratio. Main Outcomes and Measures: The primary outcome was the proportion of patients without RCDI 12 weeks after FMT. Secondary outcomes included (1) serious and minor adverse events, (2) changes in quality of life by the 36-Item Short Form Survey on a scale of 0 (worst possible quality of life) to 100 (best quality of life), and (3) patient perception on a scale of 1 (not at all unpleasant) to 10 (extremely unpleasant) and satisfaction on a scale of 1 (best) to 10 (worst). Results: Among 116 patients randomized (mean [SD] age, 58 [19] years; 79 women [68%]), 105 (91%) completed the trial, with 57 patients randomized to the capsule group and 59 to the colonoscopy group. In per-protocol analysis, prevention of RCDI after a single treatment was achieved in 96.2% in both the capsule group (51/53) and the colonoscopy group (50/52) (difference, 0%; 1-sided 95% CI, -6.1% to infinity; P < .001), meeting the criterion for noninferiority. One patient in each group died of underlying cardiopulmonary illness unrelated to FMT. Rates of minor adverse events were 5.4% for the capsule group vs 12.5% for the colonoscopy group. There was no significant between-group difference in improvement in quality of life. A significantly greater proportion of participants receiving capsules rated their experience as "not at all unpleasant" (66% vs 44%; difference, 22% [95% CI, 3%-40%]; P = .01). Conclusions and Relevance: Among adults with RCDI, FMT via oral capsules was not inferior to delivery by colonoscopy for preventing recurrent infection over 12 weeks. Treatment with oral capsules may be an effective approach to treating RCDI. Trial Registration: clinicaltrials.gov Identifier: NCT02254811.

6. Mosites, E., et al., Outbreak of Invasive Infections From Subtype emm26.3 Group A Streptococcus Among Homeless Adults-Anchorage, Alaska, 2016-2017. *Clin Infect Dis*, 2018. 66(7): p. 1068-1074.
Background: In 2016, we detected an outbreak of group A Streptococcus (GAS) invasive infections among the estimated 1000 persons experiencing homelessness (PEH) in Anchorage, Alaska. We characterized the outbreak and implemented a mass antibiotic intervention at homeless service facilities. Methods: We identified cases through the Alaska GAS laboratory-based surveillance system. We conducted emm typing, antimicrobial susceptibility testing, and whole-genome sequencing on all invasive isolates and compared medical record data of patients infected with emm26.3 and other emm types. In February 2017, we offered PEH at 6 facilities in Anchorage a single dose of 1 g of azithromycin. We collected oropharyngeal and nonintact skin swabs on a subset of participants concurrent with the intervention and 4 weeks afterward. Results: From July 2016 through April 2017, we detected 42 invasive emm26.3 cases in Anchorage, 35 of which were in PEH. The emm26.3 isolates differed on average by only 2 single-nucleotide polymorphisms. Compared to other emm types, infection with emm26.3 was associated with cellulitis (odds ratio [OR], 2.5; P = .04) and necrotizing fasciitis (OR, 4.4; P = .02). We dispensed antibiotics to 391 PEH. Colonization with emm26.3 decreased from 4% of 277 at baseline to 1% of 287 at follow-up (P = .05). Invasive GAS incidence decreased from 1.5 cases per 1000 PEH/week in the 6 weeks prior to the intervention to 0.2 cases per 1000 PEH/week in the 6 weeks after (P = .01). Conclusions: In an invasive GAS outbreak in PEH in Anchorage, mass antibiotic administration was temporally associated with reduced invasive disease cases and colonization prevalence.

7. Thwaites, G.E., et al., Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*, 2018. **391**(10121): p. 668-678.
BACKGROUND: *Staphylococcus aureus* bacteraemia is a common cause of severe community-acquired and hospital-acquired infection worldwide. We tested the hypothesis that adjunctive rifampicin would reduce bacteriologically confirmed treatment failure or disease recurrence, or death, by enhancing early *S aureus* killing, sterilising infected foci and blood faster, and reducing risks of dissemination and metastatic infection. METHODS: In this multicentre, randomised, double-blind, placebo-controlled trial, adults (>/=18 years) with *S aureus* bacteraemia who had received </=96 h of active antibiotic therapy were recruited from 29 UK hospitals. Patients were randomly assigned (1:1) via a computer-generated sequential randomisation list to receive 2 weeks of adjunctive rifampicin (600 mg or 900 mg per day according to weight, oral or intravenous) versus identical placebo, together with standard antibiotic therapy. Randomisation was stratified by centre. Patients, investigators, and those caring for the patients were masked to group allocation. The primary outcome was time to bacteriologically confirmed treatment failure or disease recurrence, or death (all-cause), from randomisation to 12 weeks, adjudicated by an independent review committee masked to the treatment. Analysis was intention to treat. This trial was registered, number ISRCTN37666216, and is closed to new participants. FINDINGS: Between Dec 10, 2012, and Oct 25, 2016, 758 eligible participants were randomly assigned: 370 to rifampicin and 388 to placebo. 485 (64%) participants had community-acquired *S aureus* infections, and 132 (17%) had nosocomial *S aureus* infections. 47 (6%) had meticillin-resistant infections. 301 (40%) participants had an initial deep infection focus. Standard antibiotics were given for 29 (IQR 18-45) days; 619 (82%) participants received flucloxacillin. By week 12, 62 (17%) of participants who received rifampicin versus 71 (18%) who received placebo experienced treatment failure or disease recurrence, or died (absolute risk difference -1.4%, 95% CI -7.0 to 4.3; hazard ratio 0.96, 0.68-1.35, p=0.81). From randomisation to 12 weeks, no evidence of differences in serious (p=0.17) or grade 3-4 (p=0.36) adverse events were observed; however, 63 (17%) participants in the rifampicin group versus 39 (10%) in the placebo group had antibiotic or trial drug-modifying adverse events (p=0.004), and 24 (6%) versus six (2%) had drug interactions (p=0.0005). INTERPRETATION: Adjunctive rifampicin provided no overall benefit over standard antibiotic therapy in adults with *S aureus* bacteraemia. FUNDING: UK National Institute for Health Research Health Technology Assessment.

8. Wiese, A.D., et al., Opioid Analgesic Use and Risk for Invasive Pneumococcal Diseases: A Nested Case-Control Study. *Ann Intern Med*, 2018. **168**(6): p. 396-404.

Background: Although certain opioid analgesics have immunosuppressive properties and increase the risk for infections in animals, the clinical effects of prescription opioid use on infection risk among humans are unknown. Objective: To test the hypothesis that prescription opioid use is an independent risk factor for invasive pneumococcal disease (IPD). Design: Nested case-control study. Setting: Tennessee Medicaid database linked to Medicare and Active Bacterial Core surveillance system databases (1995 to 2014). Patients: 1233 case patients with IPD aged 5 years and older matched to 24 399 control participants by diagnosis date, age, and county of residence. Measurements: Opioid use was measured on the basis of pharmacy prescription fills. Invasive pneumococcal disease was defined by the isolation of Streptococcus pneumoniae from a normally sterile site. The odds of current opioid use were compared between the case and control groups, accounting for known IPD risk factors. Secondary analyses categorized opioid use by opioid characteristics, applied an IPD risk score to assure comparability between exposure groups, and analyzed pneumonia and nonpneumonia IPD cases separately. Results: Persons in the case group had greater odds than control participants of being current opioid users (adjusted odds ratio [aOR], 1.62 [95% CI, 1.36 to 1.92]). Associations were strongest for opioids that were long acting (aOR, 1.87 [CI, 1.24 to 2.82]), of high potency (aOR, 1.72 [CI, 1.32 to 2.25]), or were used at high dosages (50 to 90 morphine milligram equivalents [MME]/d: aOR, 1.71 [CI, 1.22 to 2.39]; >/=90 MME/d: aOR, 1.75 [CI, 1.33 to 2.29]). Results were consistent when the IPD risk score was taken into account and pneumonia and nonpneumonia IPD were analyzed separately. Limitations: Unmeasured confounding and measurement error, although sensitivity analyses suggested that neither was likely to affect results. Actual opioid use and other nonprescription use (such as illicit opioid use) were not measured. Conclusion: Opioid use is associated with an increased risk for IPD and represents a novel risk factor for these diseases. Primary Funding Source: National Institutes of Health.

9:25 AM - 9:45 AM **4 - Transplant Infectious Diseases**

Aric Gregson; AG Infectious Disease, Los Angeles, CA

1. Aguilar-Guisado, M., et al., Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol*, 2017. **4**(12): p. e573-e583.
BACKGROUND: Continuation of empirical antimicrobial therapy (EAT) for febrile neutropenia in patients with haematological malignancies until neutrophil recovery could prolong the therapy unnecessarily. We aimed to establish whether EAT discontinuation driven by a clinical approach regardless of neutrophil recovery would optimise the duration of therapy. METHODS: We did an investigator-driven, superiority, open-label, randomised, controlled phase 4 clinical trial in six academic hospitals in Spain. Eligible patients were adults with haematological malignancies or haemopoietic stem-cell transplantation recipients, with high-risk febrile neutropenia without aetiological diagnosis. An independent, computer-generated randomisation sequence was used to randomly enrol patients (1:1) to the experimental or control group. Investigators were masked to assignment only before randomisation. EAT based on an antipseudomonal beta-lactam drug as monotherapy (ceftazidime or cefepime, meropenem or imipenem, or piperacillin-tazobactam) or as combination therapy (with an aminoglycoside, fluoroquinolone, or glycopeptide) was started according to local protocols and following international guidelines and recommendations. For the experimental group, EAT was withdrawn after 72 h or more of apyrexia plus clinical recovery; for the control group, treatment was withdrawn when the neutrophil count was also 0.5 x 10(9) cells per L or higher. The primary efficacy endpoint was the number of EAT-free days. Primary analyses were done in the intention-to-treat population. Efficacy and safety analyses were done in the intention-to-treat population and the per-protocol population. This trial is registered with ClinicalTrials.gov, number NCT01581333. FINDINGS: Between April 10, 2012, and May 31, 2016, 157 episodes among 709 patients assessed for eligibility were included in analyses. 78 patients were randomly assigned to the experimental group and 79 to the control group. The mean number of EAT-free days was significantly higher in the experimental group than in the control group (16.1 [SD 6.3] vs 13.6 [7.2], absolute difference -2.4 [95% CI -4.6 to -0.3]; p=0.026). 636 adverse events were reported (341 in the experimental group vs 295 in the control group; p=0.057) and most (580 [91%]; 323 in the experimental group vs 257 in the control group) were considered mild or moderate (grade 1-2). The most common adverse events in the experimental versus the control group were mucositis (28 [36%] of 78 patients vs 20 [25%] of 79 patients), diarrhoea (23 [29%] of 78 vs 24 [30%] of 79), and nausea and vomiting (20 [26%] of 78 vs 22 [28%] of 79). 56 severe adverse events were reported, 18 in the experimental group and 38 in the control group. One patient died in the experimental group (from hepatic veno-occlusive disease after an allogeneic haemopoietic stem-cell transplantation) and three died in the control group (one from multiorgan failure, one from invasive pulmonary aspergillosis, and one from a post-chemotherapy intestinal perforation). INTERPRETATION: In high-risk patients with haematological malignancies and febrile neutropenia, EAT can be discontinued after 72 h of apyrexia and clinical recovery irrespective of their neutrophil count. This clinical approach reduces unnecessary exposure to antimicrobials and it is safe. FUNDING: Instituto de Salud Carlos III, Spanish Ministry of Economy (PI11/02674).

2. Boeckh, M., et al., Cytomegalovirus (CMV) DNA Quantitation in Bronchoalveolar Lavage Fluid from Hematopoietic Stem Cell Transplant Recipients with CMV Pneumonia. *J Infect Dis*, 2017. **215**(10): p. 1514-1522.
Background.: Quantitative cytomegalovirus (CMV) DNA-specific polymerase chain reaction (PCR) analysis is widely used as a surveillance method for hematopoietic stem cell transplant (HCT) recipients. However, no CMV DNA threshold exists in bronchoalveolar lavage (BAL) to differentiate pneumonia from pulmonary shedding. Methods.: We tested archived BAL fluid samples from 132 HCT recipients with CMV pneumonia and 139 controls (100 patients with non-CMV pneumonia, 18 with idiopathic pneumonia syndrome [IPS], and 21 who were asymptomatic) by quantitative CMV and beta-globin DNA-specific PCR. Results.: Patients with CMV pneumonia had higher median viral loads (3.9 log10 IU/mL; interquartile range [IQR], 2.6-6.0 log10 IU/mL) than controls (0 log10 IU/mL [IQR, 0-1.6 log10 IU/mL] for patients with non-CMV pneumonia, 0 log10 IU/mL [IQR, 0-1.6 log10 IU/mL] for patients with IPS, and 1.63 log10 IU/mL [IQR, 0-2.5 log10 IU/mL] for patients who were asymptomatic; P < .001 for all comparisons to patients with CMV pneumonia). Receiver operating characteristic curve analyses and predictive models identified a cutoff CMV DNA level of 500 IU/mL to differentiate between CMV pneumonia and pulmonary shedding, using current CMV pneumonia prevalence figures. However, different levels may be appropriate in settings of very high or low CMV pneumonia prevalence. The presence of pulmonary copathogens, radiographic presentation, or pulmonary hemorrhage did not alter predictive values. Conclusion.: CMV DNA load in BAL can be used to differentiate CMV pneumonia from pulmonary shedding.

3. Camargo, J.F., et al., Impact of Cytomegalovirus Viral Load on Probability of Spontaneous Clearance and Response to Preemptive Therapy in Allogeneic Stem Cell Transplantation Recipients. *Biol Blood Marrow Transplant*, 2018. **24**(4): p. 806-814.
The optimal viral load threshold at which to initiate preemptive cytomegalovirus (CMV) therapy in hematopoietic cell transplantation (HCT) recipients remains to be defined. In an effort to address this question, we conducted a retrospective study of 174 allogeneic HCT recipients who underwent transplantation at a single center between August 2012 and April 2016. During this period, preemptive therapy was initiated at the discretion of the treating clinician. A total of 109 patients (63%) developed CMV viremia. The median time to reactivation was 17 days (interquartile range, IQR, 7-30 days) post-HCT. A peak viremia >/=150 IU/mL was strongly associated with a reduced probability of spontaneous clearance (relative risk, .16; 95% confidence interval, .1-.27), independent of established clinical risk factors, including CMV donor serostatus, exposure to antithymocyte globulin, and underlying lymphoid malignancy. The median time to clearance of viremia was significantly shorter in those who started therapy at CMV <350 IU/mL (19 days; IQR, 11-35 days) compared with those who started antiviral therapy at higher viremia thresholds (33 days; IQR, 21-42 days; P = .02). The occurrence of treatment-

associated cytopenias was frequent but similar in patients who started preemptive therapy at CMV <350 IU/mL and those who started at CMV >350 IU/mL (44% versus 57%; P = .42). Unresolved CMV viremia by treatment day 35 was associated with increased risk of therapeutic failure (32% versus 0%; P = .001). Achieving eradication of CMV viremia by treatment day 35 was associated with a 74% reduction in 1-year nonrelapse mortality (NRM) (adjusted hazard ratio [HR], .26; 95% confidence interval [CI], .1-.8; P = .02), whereas therapeutic failure was associated with a significant increase in the probability of 1-year NRM (adjusted HR, 26; 95% CI, 8-87; P <.0001). We conclude that among allogeneic HCT patients, a peak CMV viremia >/=150 IU/mL is associated with a >80% reduction in the probability of spontaneous clearance independent of ATG administration, CMV donor serostatus, and lymphoid malignancy, and is a reasonable cutoff for preemptive therapy. Delaying initiation of therapy until a CMV value >/=350 IU/mL is associated with more protracted CMV viremia, and unresolved viremia by treatment day 35 is associated with a significant increase in NRM.

4. Chamilos, G., M.S. Lionakis, and D.P. Kontoyiannis, Call for Action: Invasive Fungal Infections Associated with Ibrutinib and Other Small Molecule Kinase Inhibitors Targeting Immune Signaling Pathways. *Clin Infect Dis*, 2018. **66**(1): p. 140-148.
Opportunistic infections caused by Pneumocystis jirovecii, Cryptococcus neoformans, and ubiquitous airborne filamentous fungi have been recently reported in patients with hematological cancers historically considered at low risk for invasive fungal infections (IFIs), after receipt of the Bruton tyrosine kinase inhibitor ibrutinib. The spectrum and severity of IFIs often observed in these patients implies the presence of a complex immunodeficiency that may not be solely attributed to mere inhibition of Bruton tyrosine kinase. In view of the surge in development of small molecule kinase inhibitors for treatment of malignant and autoimmune diseases, it is possible that there would be an emergence of IFIs associated with the effects of these molecules on the immune system. Preclinical assessment of the immunosuppressive effects of kinase inhibitors and human studies aimed at improving patient risk stratification for development of IFIs could lead to prevention, earlier diagnosis, and better outcomes in affected patients.

5. Desai, A.V., et al., Exposure-Response Relationships for Isavuconazole in Patients with Invasive Aspergillosis and Other Filamentous Fungi. *Antimicrob Agents Chemother*, 2017. **61**(12).
Isavuconazole, the active moiety of the water-soluble prodrug isavuconazonium sulfate, is a triazole antifungal agent for the treatment of invasive fungal infections. The purpose of this analysis was to characterize the isavuconazole exposure-response relationship for measures of efficacy and safety in patients with invasive aspergillosis and infections by other filamentous fungi from the SECURE clinical trial. Two hundred thirty-one patients who received the clinical dosing regimen and had exposure parameters were included in the analysis. The primary drug exposure parameters included were predicted trough steady-state plasma concentrations, predicted trough concentrations after 7 and 14 days of drug administration, and area under the curve estimated at steady state (AUCss). The exposure parameters were analyzed against efficacy endpoints that included all-cause mortality through day 42 in the intent-to-treat (ITT) and modified ITT populations, data review committee (DRC)-adjudicated overall response at end of treatment (EOT), and DRC-adjudicated clinical response at EOT. The safety endpoints analyzed were elevated or abnormal alanine aminotransferase, increased aspartate aminotransferase, and a combination of the two. The endpoints were analyzed using logistic regression models. No statistically significant relationship (P > 0.05) was found between isavuconazole exposure and either efficacy or safety endpoints. The lack of association between exposure and efficacy indicates that the isavuconazole exposures achieved by clinical dosing were appropriate for treating the infecting organisms in the SECURE study and that increases in alanine or aspartate aminotransferase were not related to increase in exposures. Without a clear relationship, there is no current clinical evidence for recommending routine therapeutic drug monitoring for isavuconazole.

6. Ford, C.D., et al., Vancomycin-Resistant Enterococcus Colonization and Bacteremia and Hematopoietic Stem Cell Transplantation Outcomes. *Biol Blood Marrow Transplant*, 2017. **23**(2): p. 340-346.
The association between pre-hematopoietic stem cell transplantation (HSCT) vancomycin-resistant Enterococcus (VRE) colonization, HSCT-associated VRE bacteremia, and HSCT mortality is disputed. We studied 161 consecutive patients with acute leukemia who underwent HSCT at our hospital between 2006 and 2014, of whom 109 also received leukemia induction/consolidation on our unit. All inpatients had weekly VRE stool surveillance. Pre-HSCT colonization was not associated with increases in HSCT mortality but did identify a subgroup of HSCT recipients with a higher risk for VRE bacteremia and possibly bacteremia from other organisms. The major risk factor for pre-HSCT colonization was the number of hospital inpatient days between initial admission for leukemia and HSCT. One-third of evaluable patients colonized before HSCT were VRE-culture negative on admission for HSCT; these patients had an increased risk for subsequent VRE stool surveillance positivity but not VRE bacteremia. Molecular typing of VRE isolates obtained before and after HSCT showed that VRE strains frequently change. Postengraftment VRE bacteremia was associated with a much higher mortality than pre-engraftment VRE bacteremia. Pre-engraftment bacteremia from any organism was associated with an alternative donor and resulted in an increase in hospital length of stay and cost. Mortality was similar for pre-engraftment VRE bacteremia and pre-engraftment bacteremia due to other organisms, but mortality associated with post-engraftment VRE bacteremia was higher and largely explained by associated severe graft-versus-host disease and relapsed leukemia. These data emphasize the importance of distinguishing between VRE colonization before HSCT and at HSCT, between pre-engraftment and postengraftment VRE bacteremia, and between VRE bacteremia and bacteremia from other organisms.

7. Grimley, M.S., et al., Brincidofovir for Asymptomatic Adenovirus Viremia in Pediatric and Adult Allogeneic Hematopoietic Cell Transplant Recipients: A Randomized Placebo-Controlled Phase II Trial. *Biol Blood Marrow Transplant*, 2017. **23**(3): p. 512-521.

Adenovirus infection in immunocompromised patients contributes to significant morbidity and mortality, especially after allogeneic hematopoietic cell transplantation (HCT). Brincidofovir (BCV, CMX001) is an orally bioavailable lipid conjugate of cidofovir that has in vitro activity against adenoviruses and other double-stranded DNA viruses. This randomized placebo-controlled phase II trial evaluated pre-emptive treatment with BCV for the prevention of adenovirus disease in pediatric and adult allogeneic HCT recipients with asymptomatic adenovirus viremia. Allogeneic HCT recipients with adenovirus viremia were randomized 1:1:1 to receive oral BCV 100 mg (2 mg/kg if <50 kg) twice weekly (BIW), BCV 200 mg (4 mg/kg if <50 kg) once weekly (QW), or placebo for 6 to 12 weeks, followed by 4 weeks of post-treatment follow-up. For randomization, subjects were stratified by screening absolute lymphocyte count (<300 cells/mm(3) versus >/=300 cells/mm(3)). Assignment to BCV or placebo was double blinded; dose frequency was unblinded. The primary endpoint was the proportion of subjects experiencing treatment failure, defined as either progression to probable or definitive adenovirus disease or confirmed increasing adenovirus viremia (>/=1 log10 copies/mL) during randomized therapy. Between June 2011 and December 2012, 48 subjects were randomized to the BCV BIW (n = 14), BCV QW (n = 16), or placebo (n = 18) groups. The proportion of subjects with treatment failure in the BCV BIW group was 21% (odds ratio, .53; 95% confidence interval [CI], .11 to 2.71; P = .45), 38% (odds ratio, 1.23; 95% CI, .30 to 5.05, P = .779) in the BCV QW group, and 33% in the placebo group. All-cause mortality was lower in the BCV BIW (14%) and BCV QW groups (31%) relative to the placebo group (39%), but these differences were not statistically significant. After 1 week of therapy, 8 of 12 subjects (67%) randomized to BCV BIW had undetectable adenovirus viremia (<100 copies/mL), compared with 4 of 14 subjects (29%) randomized to BCV QW and 5 of 15 subjects (33%) randomized to placebo. In a post hoc analysis of subjects with viremia >/=1000 copies/mL at baseline, 6 of 7 BCV BIW subjects (86%) achieved undetectable viremia compared with 2 of 8 placebo subjects (25%; P = .04). Early treatment discontinuation because of adverse events was more common in subjects treated with BCV than with placebo. Diarrhea was the most common event in all groups (57% BCV BIW, 38% BCV QW, 28% placebo), but it led to treatment discontinuation in only 1 subject receiving BCV QW. Events diagnosed as acute graft-versus-host disease, primarily of the gastrointestinal tract, were more frequent in the BCV BIW group (50%) than in the BCV QW (25%) and placebo (17%) groups. There was no evidence of myelotoxicity or nephrotoxicity in BCV-treated subjects. The results of this trial confirm the antiviral activity of BCV against adenoviruses. Further investigation is ongoing to define the optimal treatment strategy for HCT recipients with serious adenovirus infection and disease.

8. Kovanda, L.L., et al., Pharmacodynamics of Isavuconazole for Invasive Mold Disease: Role of Galactomannan for Real-Time Monitoring of Therapeutic Response. *Clin Infect Dis*, 2017. **64**(11): p. 1557-1563.
Background.: The ability to make early therapeutic decisions when treating invasive aspergillosis using changes in biomarkers as a surrogate for therapeutic response could significantly improve patient outcome. Methods.: Cox proportional hazards model and logistic regression were used to correlate early changes in galactomannan index (GMI) to mortality and overall response, respectively, from patients with positive baseline GMI (>/=0.5) and serial GMI during treatment from a phase 3 clinical trial for the treatment of invasive mold disease. Pharmacokinetic/pharmacodynamic (PK/PD) analysis in patients with isavuconazole plasma concentrations was conducted to establish the exposure necessary for GMI negativity at the end of therapy. Results.: The study included 158 patients overall and 78 isavuconazole patients in the PK/PD modeling. By day 7, GMI increases of >0.25 units from baseline (3/130 survivors; 9/28 who died) significantly increased the risk of death compared to those with no increase or increases <0.25 (hazard ratio, 9.766; 95% confidence interval [CI], 4.356-21.9; P < .0001). For each unit decrease by day 7 from baseline, the odds of successful therapy doubled (odds ratio, 2.154; 95% CI, 1.173-3.955). An area under the concentration-versus-time curve over half-maximal effective concentration (AUC:EC50) of 108.6 is estimated to result in a negative GMI at the end of isavuconazole therapy. Conclusions.: Early trends in GMI are highly predictive of patient outcome. GMI increases by day 7 could be considered in context of clinical signs to trigger changes in treatment, once validated. Our data suggest that this improves survival by 10-fold and positive outcome by 3-fold. These data have important implications for individualized therapy for patients and clinical trials. Clinical Trials Registration.: NCT00412893.

9. Marty, F.M., et al., Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med, 2017. 377(25): p. 2433-2444.
BACKGROUND: Cytomegalovirus (CMV) infection remains a common complication after allogeneic hematopoietic-cell transplantation. Letermovir is an antiviral drug that inhibits the CMV-terminase complex. METHODS: In this phase 3, double-blind trial, we randomly assigned CMV-seropositive transplant recipients, 18 years of age or older, in a 2:1 ratio to receive letermovir or placebo, administered orally or intravenously, through week 14 after transplantation; randomization was stratified according to trial site and CMV disease risk. Letermovir was administered at a dose of 480 mg per day (or 240 mg per day in patients taking cyclosporine). Patients in whom clinically significant CMV infection (CMV disease or CMV viremia leading to preemptive treatment) developed discontinued the trial regimen and received anti-CMV treatment. The primary end point was the proportion of patients, among patients without detectable CMV DNA at randomization, who had clinically significant CMV infection through week 24 after transplantation. Patients who discontinued the trial or had missing end-point data at week 24 were imputed as having a primary end-point event. Patients were followed through week 48 after transplantation. RESULTS: From June 2014 to March 2016, a total of 565 patients underwent randomization and received letermovir or placebo beginning a median of 9 days after transplantation. Among 495 patients with undetectable CMV DNA at randomization, fewer patients in the letermovir group than in the placebo group had clinically significant CMV infection or were imputed as having a primary end-point event by week 24 after transplantation (122 of 325 patients [37.5%] vs. 103 of 170 [60.6%], P<0.001). The frequency and severity of adverse events were similar in the two groups overall. Vomiting was reported in 18.5% of the patients who received letermovir and in 13.5% of those who received placebo; edema in 14.5% and 9.4%, respectively; and atrial fibrillation or flutter in 4.6% and 1.0%, respectively. The rates of myelotoxic and nephrotoxic events were similar in the letermovir group and the placebo group. All-cause mortality at week 48 after transplantation was 20.9% among letermovir recipients and 25.5% among placebo recipients. CONCLUSIONS: Letermovir prophylaxis resulted in a significantly lower risk of clinically significant CMV infection than placebo. Adverse events with letermovir were mainly of low grade. (Funded by Merck; ClinicalTrials.gov number, NCT02137772 ; EudraCT number, 2013-003831-31 .).

10. Novosad, S.A., et al., *Mycoplasma hominis* Infections Transmitted through Amniotic Tissue Product. *Clin Infect Dis*, 2017.
    Background: *Mycoplasma hominis* is a commensal genitourinary tract organism that can cause infections outside the genitourinary tract. We investigated a cluster of *M. hominis* surgical site infections in patients who underwent spine surgery, all associated with amniotic tissue linked to a common donor. Methods: Laboratory tests of tissue product from the donor, including culture, quantitative real-time PCR (qPCR), and whole genome sequencing were performed. Use of this amniotic tissue product was reviewed. A multi-state investigation to identify additional cases and locate any unused products was conducted. Results: Twenty-seven tissue product vials from a donor were distributed to facilities in seven states; at least 20 vials from this donor were used in 14 patients. Of these, 4/14 (29%) developed surgical site infections, including two *M. hominis* infections. *M. hominis* was detected by culture and qPCR in two unused vials from the donor. Sequencing indicated >99% similarity between patient and unopened vial isolates. For five of 27 (19%) vials, the final disposition could not be confirmed. Conclusions: *M. hominis* was transmitted through amniotic tissue from a single donor to two recipients. Current routine donor screening and product testing does not detect all potential pathogens. Clinicians should be aware that *M. hominis* can cause surgical site infections, and may not be detected by routine clinical cultures. The lack of a standardized system to track tissue products in healthcare facilities limits the ability of public health agencies to respond to outbreaks and investigate other adverse events associated with these products.

11. Santolaya, M.E., et al., Efficacy and safety of withholding antimicrobial treatment in children with cancer, fever and neutropenia, with a demonstrated viral respiratory infection: a randomized clinical trial. *Clin Microbiol Infect*, 2017. **23**(3): p. 173-178.
    OBJECTIVES: To determine efficacy and safety of withholding antimicrobials in children with cancer, fever and neutropenia (FN) with a demonstrated respiratory viral infection. METHODS: Prospective, multicentre, randomized study in children presenting with FN at five hospitals in Santiago, Chile, evaluated at admission for diagnosis of bacterial and viral pathogens including PCR-microarray for 17 respiratory viruses. Children positive for a respiratory virus, negative for a bacterial pathogen and with a favourable evolution after 48 h of antimicrobial therapy were randomized to either maintain or withhold antimicrobials. Primary endpoint was percentage of episodes with uneventful resolution. Secondary endpoints were days of fever/hospitalization, bacterial infection, sepsis, admission to paediatric intensive care unit (PICU) and death. RESULTS: A total of 319 of 951 children with FN episodes recruited between July 2012 and December 2015 had a respiratory virus as a unique identified microorganism, of which 176 were randomized, 92 to maintain antimicrobials and 84 to withdraw. Median duration of antimicrobial use was 7 days (range 7-9 days) versus 3 days (range 3-4 days), with similar frequency of uneventful resolution (89/92 (97%) and 80/84 (95%), respectively, not significant; OR 1.48; 95% CI 0.32-6.83, p 0.61), and similar number of days of fever (2 versus 1), days of hospitalization (6 versus 6) and bacterial infections throughout the episode (2%-1%), with one case of sepsis requiring admission to PICU in the group that maintained antimicrobials, without any deaths. CONCLUSIONS: The reduction of antimicrobials in children with FN and respiratory viral infections, based on clinical and microbiological/molecular diagnostic criteria, should favour the adoption of evidence-based management strategies in this population.

12. Smibert, O.C., et al., Donor-Derived *Mycoplasma hominis* and an Apparent Cluster of *M. hominis* Cases in Solid Organ Transplant Recipients. *Clin Infect Dis*, 2017. **65**(9): p. 1504-1508.
    Background: Invasive and disseminated *Mycoplasma hominis* infections are well recognized but uncommon complications in solid organ transplant recipients. In a single center, a cluster of *M. hominis* infections were identified in lung transplant recipients from the same thoracic intensive care unit (ICU). We sought to determine the source(s) of these infections. Methods: Medical records of the donor and infected transplant recipients were reviewed for clinical characteristics. Clinical specimens underwent routine processing with subculture on *Mycoplasma*-specific Hayflick agar. *Mycoplasma hominis* identification was confirmed using sequencing of the 16S ribosomal RNA gene. *Mycoplasma hominis* isolates were subjected to whole-genome sequencing on the Illumina NextSeq platform. Results: Three lung transplant recipients presented with invasive *M. hominis* infections at multiple sites characterized by purulent infections without organisms detected by Gram staining. Each patient had a separate donor; however, pretransplant bronchoalveolar lavage fluid was only available from the donor for patient 1, which subsequently grew *M. hominis*. Phylo- and pangenomic analyses indicated that the isolates from the donor and the corresponding recipient (patient 1) were closely related and formed a distinct single clade. In contrast, isolates from patients 2 and 3 were unrelated and divergent from one another. Conclusions: *Mycoplasma hominis* should be considered a cause of donor-derived infection. Genomic data suggest donor-to-recipient transmission of *M. hominis*. Additional patients co-located in the ICU were found to have genetically unrelated *M. hominis* isolates, excluding patient-to-patient transmission.

13. Vindrios, W., et al., Outbreak of *Pneumocystis jirovecii* Infection among Heart Transplant Recipients: Molecular Investigation and Management of an Inter-human Transmission. *Clin Infect Dis*, 2017.
    Background: An outbreak of *Pneumocystis jirovecii* pneumonia (PCP) occurred among heart transplant recipients (HTR) at the outpatient clinic of a university hospital, from March to September 2015. Clinical, therapeutic, biological and molecular data were analyzed to determine its origin and control the outbreak. Methods: Clinical and biological data regarding all HTR followed in the outpatient clinic were collected. PCP diagnosis was based on microscopy and real-time PCR. Investigations were performed by building a transmission map, completed by genotyping *Pneumocystis* isolates and by a control of chemoprophylaxis observance. Asymptomatic exposed patients were screened for colonisation using real-time PCR. Results: Among 124 HTR, 7 PCP cases were confirmed. Screening identified three additional patients colonized by *Pneumocystis jirovecii*. All patients were cured and no further cases were identified after that trimethoprim-sulfamethoxazole prophylaxis was introduced in the entire cohort. Genotyping demonstrated the same strain in all PCP cases and colonized patients. All cases were linked with possible transmission chains from 2 possible index patients. Inter-human

transmission was significantly associated with more frequent visits in the outpatient clinic. Six cases were receiving atovaquone as a prophylaxis. The occurrence of PCP was significantly associated with atovaquone prophylaxis. Conclusions: This is the first outbreak with detailed molecular analysis in HTR so far. Genotyping and transmission chain confirmed the inter-human transmission in all colonized/infected PCP cases. Outpatient clinic layout and high encounters probably caused this PCP cluster, which was controlled after systematic trimethoprim-sulfamethoxazole prophylaxis in exposed patients.

14. Webb, B.J., et al., Prediction of Bloodstream Infection Due to Vancomycin-Resistant Enterococcus in Patients Undergoing Leukemia Induction or Hematopoietic Stem-Cell Transplantation. *Clin Infect Dis*, 2017. **64**(12): p. 1753-1759.
Background.: Bloodstream infection (BSI) to due vancomycin-resistant Enterococcus (VRE) is an important complication of hematologic malignancy. Determining when to use empiric anti-VRE antibiotic therapy in this population remains a clinical challenge. Methods.: A single-center cohort representing 664 admissions for induction or hematopoietic stem-cell transplant (HSCT) from 2006 to 2014 was selected. We derived a prediction score using risk factors for VRE BSI and evaluated the model's predictive performance by calculating it for each of 16232 BSI at-risk inpatient days. Results.: VRE BSI incidence was 6.5% of admissions (2.7 VRE BSI per 1000 BSI at-risk days). Adjusted 1-year mortality and length of stay were significantly higher in patients with VRE BSI. VRE colonization (adjusted odds ratio [aOR] = 8.4; 95% confidence interval [CI] = 3.4-20.6; P < .0001), renal insufficiency (aOR = 2.4; 95% CI = 1.0-5.8; P = .046), aminoglycoside use (aOR = 4.7; 95% CI = 2.2-9.8; P < .0001), and antianaerobic antibiotic use (aOR = 2.8; 95% CI = 1.3-5.8; P = .007) correlated most closely with VRE BSI. A prediction model with optimal performance included these factors plus gastrointestinal disturbance, severe neutropenia, and prior beta-lactam antibiotic use. The score effectively risk-stratified patients (area under the receiver operating curve = 0.84; 95% CI = 0.79-0.89). At a threshold of >/=5 points, per day probability of VRE BSI was increased nearly 4-fold. Conclusions.: This novel predictive score is based on risk factors reflecting a plausible pathophysiological model for VRE BSI in patients with hematological malignancy. Integrating VRE colonization status with risk factors for developing BSI is a promising method of guiding rational use of empiric anti-VRE antimicrobial therapy in patients with hematological malignancy. Validation of this novel predictive score is needed to confirm clinical utility.

15. Winston, D.J., et al., Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*, 2018. **391**(10135): p. 2116-2127.
BACKGROUND: Recipients of autologous haemopoietic stem-cell transplants (auto-HSCT) have an increased risk of herpes zoster and herpes zoster-related complications. The aim of this study was to establish the efficacy and safety of an inactivated varicella zoster vaccine for the prevention of herpes zoster after auto-HSCT. METHODS: In this randomised, double-blind, placebo-controlled phase 3 trial, participants were recruited from 135 medical centres (ie, stem-cell transplant centres and hospitals) in North America, South America, Europe, and Asia. Patients were eligible if they were aged 18 years or older, scheduled to receive an auto-HSCT within 60 days of enrolment, and had a history of varicella infection or were seropositive for antibodies to varicella zoster virus, or both. Exclusion criteria included a history of herpes zoster within the previous year of enrolment, and intended antiviral prophylaxis for longer than 6 months after transplantation. Participants were randomly assigned according to a central randomisation schedule generated by the trial statistician, to receive either the inactivated-virus vaccine from one of three consistency lots, a high-antigen lot, or placebo, stratified by age (<50 vs >/=50 years) and intended duration of antiviral prophylaxis after transplantation (</=3 months vs >3 to </=6 months). Participants, investigators, trial staff, and the funder's clinical and laboratory personnel were masked to group assignment. Participants were given four doses of inactivated vaccine or placebo, with the first dose 5-60 days before auto-HSCT, and the second, third, and fourth doses at about 30, 60, and 90 days after transplantation. The primary efficacy endpoint was the incidence of herpes zoster, confirmed by PCR or adjudication by a masked clinical committee, or both, assessed in all participants randomly assigned to the vaccine consistency lot group or placebo group who received at least one dose of vaccine and had auto-HSCT. Safety was assessed in all randomised participants who received at least one dose of vaccine and had follow-up data. A prespecified vaccine efficacy success criterion required the lower bound of the 95% CI be higher than 25% for the relative reduction of the hazard ratio of herpes zoster infection in participants given the vaccine from one of the consistency lots compared with those given placebo. This trial is registered on ClinicalTrials.gov (NCT01229267) and EudraCT (2010-020150-34). FINDINGS: Between Dec 7, 2010, and April 25, 2013, 560 participants were randomly assigned to the vaccine consistency lot group, 106 to the high-antigen lot group, and 564 to the placebo group. 249 (44%) of patients in the vaccine consistency lot group, 35 (33%) in the high-antigen lot group, and 220 (39%) in the placebo group discontinued before study end, mostly because of death or withdrawal. 51 participants were excluded from the primary efficacy endpoint analyses because they did not undergo auto-HSCT or were not vaccinated, or both (22 [4%] in the vaccine consistency lot group, and 29 [5%] in the placebo group). Mean follow-up for efficacy was 2.4 years (SD 1.3) in the vaccine consistency lot group and 2.3 years (SD 1.3) in the placebo group. 42 (8%) of 538 participants in the vaccine consistency lot group (32.9 per 1000 person-years) and 113 (21%) of 535 in the placebo group (91.9 per 1000 person-years) had a confirmed case of herpes zoster. The estimated vaccine efficacy was 63.8% (95% CI 48.4-74.6), meeting the pre-specified success criterion. For the combined vaccine groups versus the placebo group, the proportion of patients with serious adverse events (216 [33%] of 657 vs 181 [33%] of 554; risk difference 0.2%, 95% CI -5.1 to 5.5) and serious vaccine-related adverse events (five [1%] vs five [1%]; risk difference 0.1%, -1.4 to 1.1) were similar. Vaccine-related injection-site adverse events occurred more frequently in participants given vaccine than those given placebo (191 [29%] vs 36 [7%]; risk difference 22.6%, 95% CI 18.5-26.6; p<0.0001). INTERPRETATION: This study shows for the first time in a large phase 3 trial that early vaccination of auto-HSCT recipients during the peri-transplant period can be effective for the prevention of an opportunistic infection like herpes zoster and that the vaccine is well tolerated. FUNDING: Merck & Co., Inc.

16. Wolf, J., et al., Levofloxacin Prophylaxis During Induction Therapy for Pediatric Acute Lymphoblastic Leukemia. *Clin Infect Dis*, 2017. **65**(11): p. 1790-1798.
Background: Infection is the most important cause of treatment-related morbidity and mortality in pediatric patients treated for acute lymphoblastic leukemia (ALL). Although routine in adults with leukemia, antibacterial prophylaxis is controversial in pediatrics because of insufficient evidence for its efficacy or antibiotic choice and concerns about promoting antibiotic resistance and *Clostridium difficile* infection. Methods: This was a single-center, observational cohort study of patients with newly diagnosed ALL, comparing prospectively collected infection-related outcomes in patients who received no prophylaxis, levofloxacin prophylaxis, or other prophylaxis during induction therapy on the total XVI study. A propensity score-weighted logistic regression model was used to adjust for confounders. Results: Of 344 included patients, 173 received no prophylaxis, 69 received levofloxacin prophylaxis, and 102 received other prophylaxis regimens. Patients receiving prophylaxis had longer duration of neutropenia. Prophylaxis reduced the odds of febrile neutropenia, likely bacterial infection, and bloodstream infection by >/=70%. Levofloxacin prophylaxis alone reduced these infections, but it also reduced cephalosporin, aminoglycoside, and vancomycin exposure and reduced the odds of *C. difficile* infection by >95%. No increase in breakthrough infections with antibiotic-resistant organisms was seen, but this cannot be excluded. Conclusions: This is the largest study to date of antibacterial prophylaxis during induction therapy for pediatric ALL and the first to include a broad-spectrum fluoroquinolone. Prophylaxis prevented febrile neutropenia and systemic infection. Levofloxacin prophylaxis also minimized the use of treatment antibiotics and drastically reduced *C. difficile* infection. Although long-term antibiotic-resistance monitoring is needed, these data support using targeted prophylaxis with levofloxacin in children undergoing induction chemotherapy for ALL. Clinical Trials Registration: NCT00549848.

9:45 AM - 10:05 AM

5 - **HIV**

Jose Gatell; Univ. de Barcelona, Barcelona, Spain

1. Abdel-Mohsen, M., et al., CD32 is expressed on cells with transcriptionally active HIV but does not enrich for HIV DNA in resting T cells. *Sci Transl Med*, 2018. **10**(437).

The persistence of HIV reservoirs, including latently infected, resting CD4(+) T cells, is the major obstacle to cure HIV infection. CD32a expression was recently reported to mark CD4(+) T cells harboring a replication-competent HIV reservoir during antiretroviral therapy (ART) suppression. We aimed to determine whether CD32 expression marks HIV latently or transcriptionally active infected CD4(+) T cells. Using peripheral blood and lymphoid tissue of ART-treated HIV(+) or SIV(+) subjects, we found that most of the circulating memory CD32(+) CD4(+) T cells expressed markers of activation, including CD69, HLA-DR, CD25, CD38, and Ki67, and bore a TH2 phenotype as defined by CXCR3, CCR4, and CCR6. CD32 expression did not selectively enrich for HIV- or SIV-infected CD4(+) T cells in peripheral blood or lymphoid tissue; isolated CD32(+) resting CD4(+) T cells accounted for less than 3% of the total HIV DNA in CD4(+) T cells. Cell-associated HIV DNA and RNA loads in CD4(+) T cells positively correlated with the frequency of CD32(+) CD69(+) CD4(+) T cells but not with CD32 expression on resting CD4(+) T cells. Using RNA fluorescence in situ hybridization, CD32 coexpression with HIV RNA or p24 was detected after in vitro HIV infection (peripheral blood mononuclear cell and tissue) and in vivo within lymph node tissue from HIV-infected individuals. Together, these results indicate that CD32 is not a marker of resting CD4(+) T cells or of enriched HIV DNA-positive cells after ART; rather, CD32 is predominately expressed on a subset of activated CD4(+) T cells enriched for transcriptionally active HIV after long-term ART.

2. Antiretroviral Therapy Cohort, C., Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *Lancet HIV*, 2017. **4**(8): p. e349-e356.

BACKGROUND: Health care for people living with HIV has improved substantially in the past two decades. Robust estimates of how these improvements have affected prognosis and life expectancy are of utmost importance to patients, clinicians, and health-care planners. We examined changes in 3 year survival and life expectancy of patients starting combination antiretroviral therapy (ART) between 1996 and 2013. METHODS: We analysed data from 18 European and North American HIV-1 cohorts. Patients (aged >/=16 years) were eligible for this analysis if they had started ART with three or more drugs between 1996 and 2010 and had at least 3 years of potential follow-up. We estimated adjusted (for age, sex, AIDS, risk group, CD4 cell count, and HIV-1 RNA at start of ART) all-cause and cause-specific mortality hazard ratios (HRs) for the first year after ART initiation and the second and third years after ART initiation in four calendar periods (1996-99, 2000-03 [comparator], 2004-07, 2008-10). We estimated life expectancy by calendar period of initiation of ART. FINDINGS: 88 504 patients were included in our analyses, of whom 2106 died during the first year of ART and 2302 died during the second or third year of ART. Patients starting ART in 2008-10 had lower all-cause mortality in the first year after ART initiation than did patients starting ART in 2000-03 (adjusted HR 0.71, 95% CI 0.61-0.83). All-cause mortality in the second and third years after initiation of ART was also lower in patients who started ART in 2008-10 than in those who started in 2000-03 (0.57, 0.49-0.67); this decrease was not fully explained by viral load and CD4 cell count at 1 year. Rates of non-AIDS deaths were lower in patients who started ART in 2008-10 (vs 2000-03) in the first year (0.48, 0.34-0.67) and second and third years (0.29, 0.21-0.40) after initiation of ART. Between 1996 and 2010, life expectancy in 20-year-old patients starting ART increased by about 9 years in women and 10 years in men. INTERPRETATION: Even in the late ART era, survival during the first 3 years of ART continues to improve, which probably reflects transition to less toxic antiretroviral drugs, improved adherence, prophylactic measures, and management of comorbidity. Prognostic models and life expectancy estimates should be updated to account for these improvements. FUNDING: UK Medical Research Council, UK Department for International Development, EU EDCTP2 programme.

3. Bar, K.J., et al., Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption. *N Engl J Med*, 2016. **375**(21): p. 2037-2050.

BACKGROUND: The discovery of potent and broadly neutralizing antibodies (bNAbs) against human immunodeficiency virus (HIV) has made passive immunization a potential strategy for the prevention and treatment of HIV infection. We sought to determine whether passive administration of VRC01, a bNAb targeting the HIV CD4-binding site, can safely prevent or delay plasma viral rebound after the discontinuation of antiretroviral therapy (ART). METHODS: We conducted two open-label trials (AIDS Clinical Trials Group [ACTG] A5340 and National Institutes of Health [NIH] 15-I-0140) of the safety, side-effect profile, pharmacokinetic properties, and antiviral activity of VRC01 in persons with HIV infection who were undergoing interruption of ART. RESULTS: A total of 24 participants were enrolled, and one serious alcohol-related adverse event occurred. Viral rebound occurred despite plasma VRC01 concentrations greater than 50 mug per milliliter. The median time to rebound was 4 weeks in the A5340 trial and 5.6 weeks in the NIH trial. Study participants were more likely than historical controls to have viral suppression at week 4 (38% vs. 13%, P=0.04 by a two-sided Fisher's exact test in the A5340 trial; and 80% vs. 13%, P<0.001 by a two-sided Fisher's exact test in the NIH trial) but the difference was not significant at week 8. Analyses of virus populations before ART as well as before and after ART interruption showed that VRC01 exerted pressure on rebounding virus, resulting in restriction of recrudescent viruses and selection for preexisting and emerging antibody neutralization-resistant virus. CONCLUSIONS: VRC01 slightly delayed plasma viral rebound in the trial participants, as compared with historical controls, but it did not maintain viral suppression by week 8. In the small number of participants enrolled in these trials, no safety concerns were identified with passive immunization with a single bNAb (VRC01). (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTG A5340 and NIH 15-I-0140 ClinicalTrials.gov numbers, NCT02463227 and NCT02471326 .).

4. Clarridge, K.E., et al., Effect of analytical treatment interruption and reinitiation of antiretroviral therapy on HIV reservoirs and immunologic parameters in infected individuals. *PLoS Pathog*, 2018. **14**(1): p. e1006792.
Therapeutic strategies aimed at achieving antiretroviral therapy (ART)-free HIV remission in infected individuals are under active investigation. Considering the vast majority of HIV-infected individuals experience plasma viral rebound upon cessation of therapy, clinical trials evaluating the efficacy of curative strategies would likely require inclusion of ART interruption. However, it is unclear what impact short-term analytical treatment interruption (ATI) and subsequent reinitiation of ART have on immunologic and virologic parameters of HIV-infected individuals. Here, we show a significant increase of HIV burden in the CD4+ T cells of infected individuals during ATI that was correlated with the level of plasma viral rebound. However, the size of the HIV reservoirs as well as immune parameters, including markers of exhaustion and activation, returned to pre-ATI levels 6-12 months after the study participants resumed ART. Of note, the proportions of near full-length, genome-intact and structurally defective HIV proviral DNA sequences were similar prior to ATI and following reinitiation of ART. In addition, there was no evidence of emergence of antiretroviral drug resistance mutations within intact HIV proviral DNA sequences following reinitiation of ART. These data demonstrate that short-term ATI does not necessarily lead to expansion of the persistent HIV reservoir nor irreparable damages to the immune system in the peripheral blood, warranting the inclusion of ATI in future clinical trials evaluating curative strategies.

5. Gandhi, R.T., et al., Levels of HIV-1 persistence on antiretroviral therapy are not associated with markers of inflammation or activation. *PLoS Pathog*, 2017. **13**(4): p. e1006285.
Antiretroviral therapy (ART) reduces levels of HIV-1 and immune activation but both can persist despite clinically effective ART. The relationships among pre-ART and on-ART levels of HIV-1 and activation are incompletely understood, in part because prior studies have been small or cross-sectional. To address these limitations, we evaluated measures of HIV-1 persistence, inflammation, T cell activation and T cell cycling in a longitudinal cohort of 101 participants who initiated ART and had well-documented sustained suppression of plasma viremia for a median of 7 years. During the first 4 years following ART initiation, HIV-1 DNA declined by 15-fold (93%) whereas cell-associated HIV-1 RNA (CA-RNA) fell 525-fold (>99%). Thereafter, HIV-1 DNA levels continued to decline slowly (5% per year) with a half-life of 13 years. Participants who had higher HIV-1 DNA and CA-RNA before starting treatment had higher levels while on ART, despite suppression of plasma viremia for many years. Markers of inflammation and T cell activation were associated with plasma HIV-1 RNA levels before ART was initiated but there were no consistent associations between these markers and HIV-1 DNA or CA-RNA during long-term ART, suggesting that HIV-1 persistence is not driving or driven by inflammation or activation. Higher levels of inflammation, T cell activation and cycling before ART were associated with higher levels during ART, indicating that immunologic events that occurred well before ART initiation had long-lasting effects despite sustained virologic suppression. These findings should stimulate studies of viral and host factors that affect virologic, inflammatory and immunologic set points prior to ART initiation and should inform the design of strategies to reduce HIV-1 reservoirs and dampen immune activation that persists despite ART.

6. Granich, R., et al., Status and methodology of publicly available national HIV care continua and 90-90-90 targets: A systematic review. *PLoS Med*, 2017. **14**(4): p. e1002253.
BACKGROUND: In 2014, the Joint United Nations Program on HIV/AIDS (UNAIDS) issued treatment goals for human immunodeficiency virus (HIV). The 90-90-90 target specifies that by 2020, 90% of individuals living with HIV will know their HIV status, 90% of people with diagnosed HIV infection will receive antiretroviral treatment (ART), and 90% of those taking ART will be virally suppressed. Consistent methods and routine reporting in the public domain will be necessary for tracking progress towards the 90-90-90 target. METHODS AND FINDINGS: For the period 2010-2016, we searched PubMed, UNAIDS country progress reports, World Health Organization (WHO), UNAIDS reports, national surveillance and program reports, United States President's Emergency Plan for AIDS Relief (PEPFAR) Country Operational Plans, and conference presentations and/or abstracts for the latest available national HIV care continuum in the public domain. Continua of care included the number and proportion of people living with HIV (PLHIV) who are diagnosed, on ART, and virally suppressed out of the estimated number of PLHIV. We ranked the described methods for indicators to derive high-, medium-, and low-quality continuum. For 2010-2016, we identified 53 national care continua with viral suppression estimates representing 19.7 million (54%) of the 2015 global estimate of PLHIV. Of the 53, 6 (with 2% of global burden) were high quality, using standard surveillance methods to derive an overall denominator and program data from national cohorts for estimating steps in the continuum. Only nine countries in sub-Saharan Africa had care continua with viral suppression estimates. Of the 53 countries, the average proportion of the aggregate of PLHIV from all countries on ART was 48%, and the proportion of PLHIV who were virally suppressed was 40%. Seven countries (Sweden, Cambodia, United Kingdom, Switzerland, Denmark, Rwanda, and Namibia) were within 12% and 10% of achieving the 90-90-90 target for "on ART" and for "viral suppression," respectively. The limitations to consider when interpreting the results include significant variation in methods used to determine national continua and the possibility that complete continua were not available through our comprehensive search of the public domain. CONCLUSIONS: Relatively few complete national continua of care are available in the public domain, and there is considerable variation in the methods for determining progress towards the 90-90-90 target. Despite bearing the highest HIV burden, national care continua from sub-Saharan Africa were less likely to be in the public domain. A standardized monitoring and evaluation approach could improve the use of scarce resources to achieve 90-90-90 through improved transparency, accountability, and efficiency.

7. Huot, N., et al., Natural killer cells migrate into and control simian immunodeficiency virus replication in lymph node follicles in African green monkeys. *Nat Med*, 2017. **23**(11): p. 1277-1286.
Natural killer (NK) cells play an essential role in antiviral immunity, but knowledge of their function in secondary lymphoid organs is incomplete. Lymph node follicles constitute a major viral reservoir during infections with HIV-1 and simian immunodeficiency virus

of macaques (SIVmac). In contrast, during nonpathogenic infection with SIV from African green monkeys (SIVagm), follicles remain generally virus free. We show that NK cells in secondary lymphoid organs from chronically SIVagm-infected African green monkeys (AGMs) were frequently CXCR5(+) and entered and persisted in lymph node follicles throughout the follow-up (240 d post-infection). These follicles were strongly positive for IL-15, which was primarily presented in its membrane-bound form by follicular dendritic cells. NK cell depletion through treatment with anti-IL-15 monoclonal antibody during chronic SIVagm infection resulted in high viral replication rates in follicles and the T cell zone and increased viral DNA in lymph nodes. Our data suggest that, in nonpathogenic SIV infection, NK cells migrate into follicles and play a major role in viral reservoir control in lymph nodes.

8. Koullias, Y., et al., Should We Be Testing for Baseline Integrase Resistance in Patients Newly Diagnosed with Human Immunodeficiency Virus? *Clin Infect Dis*, 2017. **65**(8): p. 1274-1281.

Background: Current guidelines recommend genotype resistance testing at diagnosis to guide initial selection of antiretroviral therapy (ART). Many standard resistance genotypes exclude testing for resistance to integrase inhibitors ("IR testing"), although this class of drugs is a component of most recommended first-line regimens. Methods: We compared the 96-week clinical outcomes and cost-effectiveness of 2 strategies: no IR testing vs IR testing performed at human immunodeficiency virus (HIV) diagnosis. The base case prevalence of transmitted integrase strand transfer inhibitor (INSTI)-resistant (INSTI-R) virus is estimated at 0.1%. With no IR testing, all patients start dolutegravir (DTG)-based ART after genotype; 12-week suppression rates are 90% (INSTI-susceptible [INSTI-S] virus) and 35% (INSTI-R virus). Those not suppressed at 12 weeks undergo IR testing; if diagnosed with INSTI-R virus, they change to ritonavir-boosted darunavir (DRV/r)-based ART. With IR testing, all patients are diagnosed with INSTI-S/INSTI-R virus prior to ART initiation and start DTG- or DRV/r-based regimens, respectively. Costs include IR tests (175 US dollars [USD]) and ART (41100-44900 USD/year). We examined the impact of key parameters in sensitivity analyses. Results: IR testing resulted in worse clinical outcomes compared to no IR testing and increased costs by 200 USD/person/year. Prevalence of transmitted INSTI-R virus did not affect the favored strategy. No IR testing remained clinically preferred unless DTG suppression of INSTI-R virus was <20% or 96-week DRV/r suppression was >92%. If quality of life was worse with DRV/r- than DTG-based ART, no IR testing was clinically preferred over an even broader range of parameters. Conclusions: In patients with newly diagnosed HIV, IR testing is projected to result in worse outcomes and is not cost-effective. Pretreatment assessment for INSTI resistance should not be recommended in treatment guidelines.

10:25 AM - 10:45 AM

6 - Infectious Diseases Diagnostics

Lars Westblade; Cornell Univ., New York, NY

1. Balmaseda, A., et al., Comparison of Four Serological Methods and Two Reverse Transcription-PCR Assays for Diagnosis and Surveillance of Zika Virus Infection. *J Clin Microbiol*, 2018. **56**(3).
Zika virus (ZIKV) is a mosquito-borne flavivirus that is responsible for recent explosive epidemics in the Americas. Notably, ZIKV infection during pregnancy has been found to cause congenital birth defects, including microcephaly, and ZIKV has been associated with Guillain-Barre syndrome in adults. Diagnosis and surveillance of Zika in the Americas have been challenging due to similar clinical manifestations and extensive antibody cross-reactivity with endemic flaviviral diseases, such as dengue. We evaluated four serological and two reverse transcription-PCR (RT-PCR) methods in acute-phase (mean day, 1.8), early-convalescent-phase (mean day, 16.7), and late-convalescent-phase (mean, ~7 months) samples from the same individuals in a long-term pediatric cohort study in Nicaragua. Well-characterized samples from 301 cases of Zika, dengue, or non-Zika, nondengue febrile illnesses were tested. Compared to a composite reference, an in-house IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) and the NIAID-Biodefense and Emerging Infections (BEI) MAC-ELISA measuring IgM yielded sensitivities of 94.5% and 70.1% and specificities of 85.6% and 82.8%, respectively. The NS1 blockade-of-binding ELISA measuring anti-ZIKV NS1 antibody levels yielded sensitivities of 85.0% and 96.5% and specificities of 91.4% and 92.6% at early and late convalescence, respectively. An inhibition ELISA detecting total anti-ZIKV antibodies had sensitivity and specificity values of 68.3% and 58.3% for diagnosis and 94.0% and 98.6% for measuring annual infection incidence. Finally, the ZCD and Trioplex real-time RT-PCR assays detecting Zika, chikungunya, and dengue viruses both yielded a sensitivity of 96.1% and specificity of 100%. Together, these assays resolve the urgent need for diagnostic and surveillance tools for countries affected by Zika virus infections.

2. Chakravorty, S., et al., The New Xpert MTB/RIF Ultra: Improving Detection of Mycobacterium tuberculosis and Resistance to Rifampin in an Assay Suitable for Point-of-Care Testing. *MBio*, 2017. **8**(4).
The Xpert MTB/RIF assay (Xpert) is a rapid test for tuberculosis (TB) and rifampin resistance (RIF-R) suitable for point-of-care testing. However, it has decreased sensitivity in smear-negative sputum, and false identification of RIF-R occasionally occurs. We developed the Xpert MTB/RIF Ultra assay (Ultra) to improve performance. Ultra and Xpert limits of detection (LOD), dynamic ranges, and RIF-R rpoB mutation detection were tested on Mycobacterium tuberculosis DNA or sputum samples spiked with known numbers of M. tuberculosis H37Rv or Mycobacterium bovis BCG CFU. Frozen and prospectively collected clinical samples from patients suspected of having TB, with and without culture-confirmed TB, were also tested. For M. tuberculosis H37Rv, the LOD was 15.6 CFU/ml of sputum for Ultra versus 112.6 CFU/ml of sputum for Xpert, and for M. bovis BCG, it was 143.4 CFU/ml of sputum for Ultra versus 344 CFU/ml of sputum for Xpert. Ultra resulted in no false-positive RIF-R specimens, while Xpert resulted in two false-positive RIF-R specimens. All RIF-R-associated M. tuberculosis rpoB mutations tested were identified by Ultra. Testing on clinical sputum samples, Ultra versus Xpert, resulted in an overall sensitivity of 87.5% (95% confidence interval [CI], 82.1, 91.7) versus 81.0% (95% CI, 74.9, 86.2) and a sensitivity on sputum smear-negative samples of 78.9% (95% CI, 70.0, 86.1) versus 66.1% (95% CI, 56.4, 74.9). Both tests had a specificity of 98.7% (95% CI, 93.0, 100), and both had comparable accuracies for detection of RIF-R in these samples. Ultra should significantly improve TB detection, especially in patients with paucibacillary disease, and may provide more-reliable RIF-R detection.IMPORTANCE The Xpert MTB/RIF assay (Xpert), the first point-of-care assay for tuberculosis (TB), was endorsed by the World Health Organization in December 2010. Since then, 23 million Xpert tests have been procured in 130 countries. Although Xpert showed high overall sensitivity and specificity with pulmonary samples, its sensitivity has been lower with smear-negative pulmonary samples and extrapulmonary samples. In addition, the prediction of rifampin resistance (RIF-R) in paucibacillary samples and for a few rpoB mutations has resulted in both false-positive and false-negative results. The present study is the first demonstration of the design features and operational characteristics of an improved Xpert Ultra assay. This study also shows that the Ultra format overcomes many of the known shortcomings of Xpert. The new assay should significantly improve TB detection, especially in patients with paucibacillary disease, and provide more-reliable detection of RIF-R.

3. Cybulski, R.J., Jr., et al., Clinical impact of a Multiplex Gastrointestinal PCR Panel in Patients with Acute Gastroenteritis. *Clin Infect Dis*, 2018.
Background: Molecular syndromic diagnostic panels can enhance pathogen identification in the approximately 2-4 billion episodes of acute gastroenteritis that occur annually worldwide. However, the clinical utility of these panels has not been established. Methods: We conducted a prospective, multi-center study to investigate the impact of the BioFire FilmArray Gastrointestinal PCR panel on clinical diagnosis and decision-making and compared the clinical acuity of patients with positive results obtained exclusively with the FilmArray with those detected by conventional stool culture. A total of 1,887 consecutive fecal specimens were tested in parallel by FilmArray and stool culture. Laboratory and medical records were reviewed to determine rates of detection, turnaround times, clinical features and the nature and timing of clinical decisions. Results: FilmArray detected pathogens in 35.3% of specimens, compared to 6.0% for culture. Median time from collection to result was 18h for FilmArray and 47h for culture. Median time from collection to initiation of antimicrobial therapy was 22h for FilmArray and 72h for culture. Patients diagnosed by FilmArray were more likely to receive targeted rather than empirical therapy, compared to those diagnosed by culture (p=0.0148). Positive STEC results were reported 47h faster with FilmArray and facilitated discontinuation of empirical antimicrobials. Patients diagnosed exclusively by FilmArray had clinical characteristics similar to those identified by culture. Conclusions: FilmArray markedly improved clinical sensitivity in patients with acute diarrhea, identified cases with clinical acuity comparable to those identified by culture, and enabled clinicians to make more timely and targeted therapeutic decisions.

4. Kriegeskorte, A., et al., Comparison of Different Phenotypic Approaches to Screen and Detect mecC-Harboring Methicillin-Resistant *StaphylococcuS aureus*. *J Clin Microbiol*, 2018. **56**(1).
Similar to *mecA*, *mecC* confers resistance against beta-lactams, leading to the phenotype of methicillin-resistant *Staphylococcus aureus* (MRSA). However, *mecC*-harboring MRSA strains pose special difficulties in their detection. The aim of this study was to assess and compare different phenotypic systems for screening, identification, and susceptibility testing of *mecC*-positive MRSA isolates. A well-characterized collection of *mecC*-positive *S. aureus* isolates (n = 111) was used for evaluation. Routinely used approaches were studied to determine their suitability to correctly identify *mecC*-harboring MRSA, including three (semi)automated antimicrobial susceptibility testing (AST) systems and five selective chromogenic agar plates. Additionally, a cefoxitin disk diffusion test and an oxacillin broth microdilution assay were examined. All *mecC*-harboring MRSA isolates were able to grow on all chromogenic MRSA screening plates tested. Detection of these isolates in AST systems based on cefoxitin and/or oxacillin testing yielded overall positive agreements with the *mecC* genotype of 97.3% (MicroScan WalkAway; Siemens), 91.9% (Vitek 2; bioMerieux), and 64.9% (Phoenix, BD). The phenotypic resistance pattern most frequently observed by AST devices was "cefoxitin resistance/oxacillin susceptibility," ranging from 54.1% (Phoenix) and 83.8% (Vitek 2) to 92.8% (WalkAway). The cefoxitin disk diffusion and oxacillin broth microdilution assays categorized 100% and 61.3% of isolates to be MRSA, respectively. The chromogenic media tested confirmed their suitability to reliably screen for mecC-harboring MRSA. The AST systems showed false-negative results with varying numbers, misidentifying *mecC*-harboring MRSA as methicillin-susceptible *S. aureus*. This study underlines cefoxitin's status as the superior surrogate *mecC*-positive MRSA marker.

5. Liesman, R.M., et al., Evaluation of a Commercial Multiplex Molecular Panel for Diagnosis of Infectious Meningitis and Encephalitis. *J Clin Microbiol*, 2018. **56**(4).
Rapid and accurate laboratory tests are important for the timely diagnosis and treatment of central nervous system infections. The FilmArray meningitis/encephalitis (ME) panel (BioFire Diagnostics, Salt Lake City, UT) is an FDA-cleared, multiplex molecular panel that allows the detection of 14 pathogens (bacterial [n = 6], viral [n = 7], and fungal [n = 1] pathogens) from cerebrospinal fluid (CSF). In this study, we evaluated the performance characteristics of the FilmArray ME panel using clinical, residual CSF samples (n = 291) that tested positive by a routine method(s) (e.g., bacterial culture, individual real-time PCR assay) for a pathogen represented on the ME panel. Of note, a subset (n = 76) of the CSF specimens was collected during the prevaccine era and had been characterized as positive for a bacterial pathogen. The FilmArray ME panel demonstrated an overall percent positive agreement (PPA) of 97.5% (78/80) for bacterial pathogens, 90.1% (145/161) for viruses, and 52% (26/50) for Cryptococcusneoformans/C. gattii Despite the low overall agreement (52%) between the ME panel and antigen testing for detection of C. neoformans/C. gattii, the percent positive agreement of the FilmArray assay for C. neoformans/C. gattii was 92.3% (12/13) when the results were compared directly to the results of routine fungal smear or culture. The FilmArray ME panel offers a rapid (approximately 60-min), syndrome-based approach for the detection of select meningitis and encephalitis pathogens.

6. Pancholi, P., et al., Multicenter Evaluation of the Accelerate PhenoTest BC Kit for Rapid Identification and Phenotypic Antimicrobial Susceptibility Testing Using Morphokinetic Cellular Analysis. *J Clin Microbiol*, 2018.
We describe results from a multicenter study evaluating the Accelerate Pheno system, a first of its kind diagnostic system that rapidly identifies common bloodstream pathogens from positive blood cultures within 90 minutes and determines bacterial phenotypic antimicrobial susceptibility testing (AST) results within approximately seven h. A combination of fresh clinical and seeded blood cultures were tested and results from the Accelerate Pheno system were compared to VITEK(R) 2 for identification (ID) and broth microdilution or disk diffusion for AST. The Accelerate Pheno system accurately identified 14 common bacterial pathogens and two Candida spp. with sensitivities ranging from 94.6-100%. Of fresh positive blood cultures, 89% received a monomicrobial call with a positive predictive value of 97.3%.Six common Gram-positive cocci were evaluated for ID. Five were tested against eight antibiotics and two resistance-phenotypes [lsqb]methicillin resistant Staphylococcu*S aureus* and Staphylococcus spp. (MRSA/MRS) and inducible clindamycin resistance (MLSb)[rsqb]. From the 4,142 AST results, the overall essential agreement (EA) and categorical agreement (CA) were 97.6% and 97.9%, respectively. Overall very major (VME), major (ME) and minor (mE) error rates were 1.0%, 0.7% and 1.3%, respectively.Eight species of Gram-negative rods were evaluated against 15 antibiotics. From the 6,331 AST results, overall EA and CA were 95.4% and 94.3%, respectively. Overall VME, ME and mE rates were 0.5%, 0.9% and 4.8%, respectively. The Accelerate Pheno system has the unique ability to identify and provide phenotypic minimum inhibitory concentration and categorical AST results in a few hours directly from positive blood culture bottles and support accurate antimicrobial adjustment.

7. Smith, K.P., A.D. Kang, and J.E. Kirby, Automated Interpretation of Blood Culture Gram Stains by Use of a Deep Convolutional Neural Network. *J Clin Microbiol*, 2018. **56**(3).
Microscopic interpretation of stained smears is one of the most operator-dependent and time-intensive activities in the clinical microbiology laboratory. Here, we investigated application of an automated image acquisition and convolutional neural network (CNN)-based approach for automated Gram stain classification. Using an automated microscopy platform, uncoverslipped slides were scanned with a 40x dry objective, generating images of sufficient resolution for interpretation. We collected 25,488 images from positive blood culture Gram stains prepared during routine clinical workup. These images were used to generate 100,213 crops containing Gram-positive cocci in clusters, Gram-positive cocci in chains/pairs, Gram-negative rods, or background (no cells). These categories were targeted for proof-of-concept development as they are associated with the majority of bloodstream infections. Our CNN model achieved a classification accuracy of 94.9% on a test set of image crops. Receiver operating characteristic (ROC) curve analysis indicated a robust ability to differentiate between categories with an area under the curve of >0.98 for each. After training

and validation, we applied the classification algorithm to new images collected from 189 whole slides without human intervention. Sensitivity and specificity were 98.4% and 75.0% for Gram-positive cocci in chains and pairs, 93.2% and 97.2% for Gram-positive cocci in clusters, and 96.3% and 98.1% for Gram-negative rods. Taken together, our data support a proof of concept for a fully automated classification methodology for blood-culture Gram stains. Importantly, the algorithm was highly adept at identifying image crops with organisms and could be used to present prescreened, classified crops to technologists to accelerate smear review. This concept could potentially be extended to all Gram stain interpretive activities in the clinical laboratory.

8. Thoendel, M., et al., Identification of Prosthetic Joint Infection Pathogens Using a Shotgun Metagenomics Approach. *Clin Infect Dis*, 2018.

Background: Metagenomic shotgun sequencing has the potential to change how many infections, particularly those caused by difficult to culture organisms, are diagnosed. Metagenomics was used to investigate prosthetic joint infections (PJIs), where pathogen detection can be challenging. Methods: 408 sonicate fluid samples generated from resected hip and knee arthroplasties were tested, including 213 from subjects with infections and 195 from subjects without infection. Samples were enriched for microbial DNA using the MolYsis basic kit, whole-genome amplified, and sequenced using Illumina HiSeq 2500 instruments. A pipeline was designed to screen out human reads and analyze remaining sequences for microbial content using the Livermore Metagenomics Analysis Toolkit (LMAT) and MetaPhlAn2 tools. Results: When compared to sonicate fluid culture, metagenomics was able to identify known pathogens in 94.8% (109/115) of culture-positive PJIs, with additional potential pathogens detected in 9.6% (11/115). New potential pathogens were detected in 43.9% (43/98) of culture-negative PJIs, 21 of which had no other positive culture sources from which these microorganisms had been detected. Detection of microorganisms in samples from uninfected aseptic failure cases was conversely rare (7/195 or 3.6% of cases). The presence of human and contaminant microbial DNA from reagents was a challenge, as previously reported. Conclusions: Metagenomic shotgun sequencing is a powerful tool to identify a wide range of PJI pathogens, including difficult to detect pathogens in culture-negative infections.