crisis of antibacterial resistance. Little is known about the genomic traits of the infant resistome, especially in areas with high endemic antibacterial resistance.

***Methods.*** We analyzed ARGs among a subset of infants from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) birth cohort. The subset included 75 mostly term, healthy Singaporean infants born from November 2009 to May 2011. Stool samples collected at Week 3 (W3), months 3 (M3), 6 (M6) and 12 (M12) were analyzed using shotgun metagenomics. Sequencing reads were assembled into contigs using MEGAHIT. ARGs were identified using ResFinder 2.1. Demographic, perinatal factors, pre- and postnatal antibiotic exposure were collected.

***Results.*** One hundred and eighty-eight stool samples from 75 infants were studied. Of the 169 ARGs detected, the four commonest ARGs were blaZ, fosA, tet(M) and mef(A), conferring resistance to β-lactams, fosfomycin, tetracyclines, and macrolides respectively. The number of ARGs per infant increased over time (median: W3 = 18.0, M12 = 22.0, $P < 0.05$). At W3, 118 ARGs were detected among 28 infants. The most prevalent ARGs were fos(A) and blaZ (both 96.4%) at W3. Among the 22 infants who had samples at W3 and M12, only six of 118 ARGs detected at W3 were also present at M12. These were mef(A), msr(D), tet(W), erm(B), tet(M) and fosA, conferring macrolide and tetracycline resistance. Their prevalence among at M12 was 100%, 93.3%, 90.9%, 84.6%, 68.8% and 52.4%, respectively. ARGs were not associated with gender, race, delivery mode, peripartum or postnatal antibiotics in infancy. Of note, longitudinal analysis showed that only the cfxA gene, which confers β-lactam resistance, was more prevalent in infants whose mothers received antibiotics in pregnancy than those whose mothers did not (adjusted $P < 0.05$).

***Conclusion.*** In regions with high endemic antimicrobial resistance such as Singapore, the infant gut harbors a diversity of ARGs as early as 3 weeks of age. Few ARGs persisted through infancy, implying the dynamic nature of the infant resistome. The lack of association of ARGs with most clinical variables evaluated here suggests that other unrecognized factors may contribute to the plasticity of ARGs in the infant gut resistome.

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### 624. Microbiota and Associations with Treatment Outcome in Fecal Microbiota Transplantation

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**Session:** 64. Microbiome and Beyond
*Thursday, October 4, 2018: 12:30 PM*

***Background.*** Fecal microbiota transplantation (FMT) can be an effective treatment of recurrent *Clostridium difficile* infection (CDI), although non-responsiveness to treatment remains poorly understood. Here we examine the bacterial composition of stool from FMT recipients using culture-independent methods to identify associations between bacterial community structure, route of FMT administration (colonoscopy or freeze-dried encapsulated FMT (capsules)), treatment outcome and donor. We hypothesized that multiple community structures could be associated with and may better define treatment outcome.

***Methods.*** We tested this hypothesis by analyzing bacterial composition profiles and their relationship with treatment route, outcome and donor using bioinformatics and multivariate statistics on 16S rRNA gene sequences (16S) from 21 individuals (seven male, 14 female, median 68 years) with recurrent CDI prior to and after FMT. Successful endpoint was defined as no relapse of *C. difficile* associated diarrhea during 12 weeks post-FMT. There were 17 successes (four colonoscopy, 13 capsules) and four failures (all capsules). Analyses of 16S profiles included permutational analysis of variance (PERMANOVA) and linear regression models applied to bacterial abundances and diversity (as responses).

***Results.*** Significant differences were determined between pre- and post-FMT successes and failures ($P < 1e^{-4}$, $R^2 = 0.24$). No differences were seen between route ($P = 0.15$) or donor ($P = 0.20$). Profiles of failed FMT recipients were more similar to pre-FMT profiles by multidimensional scaling. Analyses of changes in abundance of pre-FMT profiles vs. outcome, controlled for age and sex, identified significant ($P < 0.01$) differences across 19 of the 25 most abundant taxa. Of the five most abundant taxa, Enterobacteriaceae and *Esherichia-Shigella* decreased significantly in successful outcomes, while *Faecalibacterium*, *Blautia*, and *Bacteroides* increased. However, variation in individual composition was also significant suggesting that multiple profiles represent successful outcomes.

***Conclusion.*** Increases in microbiota diversity are generally achieved in successful FMT regardless of administration route, although more than one bacterial composition profile can be identified.

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

### 625. Metabolic Interactions Drive *Staphylococcus aureus* Adaptation to the Skin

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**Session:** 65. Pathogenesis and Immune Response
*Thursday, October 4, 2018: 12:30 PM*

***Background.*** *Staphylococcus aureus* is the most common pathogen causing skin and soft-tissue infection and poses a particular problem to patients with atopic dermatitis who have increased colonization and infection rates. *S. aureus* is a versatile pathogen that adapts to the relatively hypoxic environment of the skin, although the underlying mechanisms of adaptation remain unclear. We hypothesized that adaptation to the skin is largely driven by metabolic interactions between *S. aureus* and keratinocytes.

***Methods.*** We characterized 10 clinical *S. aureus* isolates obtained from individual patients with atopic dermatitis using whole genome sequencing and qRT-PCR to evaluate their genotypic and phenotypic properties. The metabolic and inflammatory responses of keratinocytes to *S. aureus* infection were assessed *in vitro* in primary human keratinocytes and *in vivo* in a murine cutaneous abscess model.

***Results.*** Host-adapted *S. aureus* isolates from atopic dermatitis patients are phylogenetically diverse and are associated with varying severity of disease. They stimulate glycolysis and stabilize HIF1α in keratinocytes, and produce a similar infectious phenotype to WT USA300 LAC in a murine cutaneous abscess model. Numerous metabolic nonsynonymous mutations in genes encoding glycolytic and TCA cycle enzymes were identified in these strains. Increased expression of *fumC*, that encodes fumarase which hydrates fumarate to malate in the TCA cycle, was observed in the clinical isolates compared with WT LAC. Based on this finding and recent literature demonstrating that fumarate accumulation in immune cells is vital for trained immunity and that it inhibits glycolysis via GAPDH inactivation, we hypothesized that host-adapted *S. aureus* strains upregulate fumarase in response to increased fumarate levels in the skin. Keratinocytes infected with our clinical strains secrete increased fumarate compared with uninfected keratinocytes.

***Conclusion.*** *S. aureus* strains from atopic dermatitis skin represent a diverse population that are unified in their ability to adapt via metabolic interactions with keratinocytes. They adapt to increased fumarate levels in the skin by upregulating fumarase which likely represents a feedback inhibitory response to increased glycolysis in keratinocytes.

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

### 626. An Inexpensive Quantitative Method for Testing Anti-Fungal Drug Activity Using the Invertebrate *Caenorhabditis elegans*

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**Session:** 65. Pathogenesis and Immune Response
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***Background.*** Due to ethical and budgetary concerns associated with the use of vertebrate animals in research, interest in alternative models has increased over the past several decades. In the present study, we developed a *Candida albicans* quantitative infection model in *Caenorhabditis elegans*, a nonparasitic invertebrate nematode, to test the antifungal effects of liposomal amphotericin B (L-AmB).

***Methods.*** To establish a lethal *C. albicans* infection, larval Stage 4 worms [$n = 30$/group (gp)] were fed various doses of yeast ($2.5 \times 10^2$–$2.5 \times 10^5$ cells/gp) for 4 hours at 20°C or 30°C. The infection was evaluated by monitoring worms for mortality and determining fungal burden in worm homogenates by plating for colony forming units every 24 hours for 4 days post-challenge. To examine the worm's ability to ingest L-AmB and to determine drug toxicity, uninfected worms were fed L-AmB (6.3–25 μg/gp) for 4 hours at 30°C, and drug toxicity evaluated by survival with drug concentrations determined by bioassay of worm homogenates. The lack of toxicity allowed us to evaluate L-AmB activity in worms challenged for 4 hours at 30°C with $2.5 \times 10^5$ yeast cells/gp and then treated with L-AmB (0.5–25 ug/gp) for 4 hours at 30°C, with survival rate and fungal burden to assess L-AmB treatment.

***Results.*** *Calbicans* infection was established in worms challenged with all yeast doses, with optimum infection observed with $2.5 \times 10^5$ yeast cells/gp at 30°C (13% survival in-infected worms vs. 87% in uninfected worms). We observed that uninfected worms could take up L-AmB at doses of 6.3–25 μg/gp and yet was not toxic for the worms (93–95% survival). In worms exposed to yeast and treated with L-AmB, complete clearance of infection was achieved with the higher doses (6.3–25 μg/gp), while lower doses (1.6–3.1 μg/gp) significantly reduced the fungal burden ($P \leq 0.05$). Infected worms, not treated with L-AmB had only 10% survival, while L-AmB improved survival in a dose-dependent manner giving 40% survival for 0.5 μg L-AmBi/gp and 100% survival for doses of 6.3 μg/gp and higher.

***Conclusion.*** By using fungal burden as a readout of efficacy, along with survival, we have established a quantitative, reproducible, flexible method for examining the activity of L-AmB in *C. elegans* which could be expanded for use in evaluating other antifungal drugs and different pathogenic fungi.

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

### 627. Differences in *C. difficile* Toxin A Binding in Humans: Adults vs. Infants

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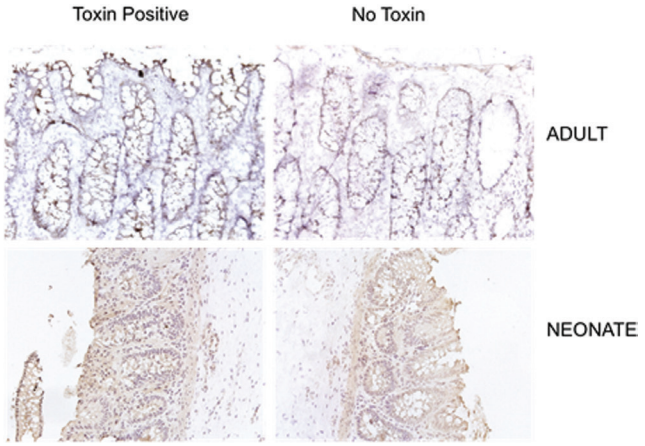
***Background.*** Children less than 1 year of age are commonly colonized with toxin-producing *C. difficile*, but appear to be immune to the associated colitis. Animal studies suggest that young infants lack receptors for *C. difficile* toxin, though this has never been documented in humans.

***Methods.*** Tissue from infants (<6 months) and adults > 21 years were studied. Toxin A binding was assessed using an indirect staining method, which included incubation with toxin A (List Labs) and detection with a rabbit polyclonal anti-sera (Lee Labs). A trained pediatric pathologist assessed the extent of staining in a blinded fashion. In other studies, toxin A was labeled with rhenium-188 and incubated with albumin-blocked tissue sections (four-infant and six-adult) for 1 hour. After washing, gamma counts were measured and the average percentage of retained radiolabeled toxin A calculated. Fisher exact tests and ANOVA were used for analyses. All studies were done in compliance with our institutional IRB.

***Results.*** Six of 13 (46%) adult specimens were found to have reactivity on both the apical epithelial surface as well as crypt staining. Another six had reactivity localized only to the basal and lateral surface of the crypts. One specimen demonstrated no reactivity at all. For neonates ($n = 15$), no specimens were found to have reactivity localized to the apical epithelial surface, though four specimens had reactivity at the basal epithelial surface ($P$ value for comparison of apical staining 0.0046) (see figure). Average percentage of retained counts for control (no tissue), infant and adult colon sections were, 0.318 ± 0.147, 0.305 ± 0.079 and 0.48 ± 0.114, respectively ($P = 0.051$).




***Conclusion.*** Immunohistochemistry and radiolabelling studies indicate that neonatal colon section binds *C. difficile* toxin A less strongly and in a different distribution pattern (i.e., without apical staining) when compared with adult colon sections. These findings are consistent with previous animal studies and support the paradigm that a lack of toxin receptors in the infant colon contributes to immunity against *C. difficile* colitis. Additional studies are needed to define the presence of specific receptors and determine if a similar phenomenon applies to toxin B binding.

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

### 628. Short-Term Water-Pipe (Shisha) Smoke Exposure Worsens Lung Inflammation in Mice Infected with Respiratory Syncytial Virus

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***Background.*** Water-pipe smoking (WPS) is becoming popular all over the world and among various populations despite the growing concern about the associated deleterious health effects. Chronic cigarette smoke exposure enhances respiratory syncytial virus (RSV) pathology in mouse airways. However, the effects of exposure to WPS on the course of RSV are not known. Here, we examined the impact of short-term WPS exposure on the course of RSV in a mouse model.

***Methods.*** BALB/c mice were exposed to nose-only mainstream WPS for 30 min/day for 4 consecutive days. Control mice were exposed with the same regimen to air only. At the end of the exposure period, WPS-exposed and control mice were intranasally inoculated with RSV A2 strain. The mice were sacrificed on selected days post-infection. Several endpoints including body weight, markers of inflammation (tumor necrosis factor-α [TNF-α] and interleukin 1β [IL1β]) and oxidative stress (superoxide dismutase [SOD]), histopathology and lung viral copies were evaluated.

***Results.*** On Day 3 post-infection, mice exposed to WPS and infected with RSV exhibited significant weight loss in comparison to control mice ($P = 0.002$), Figure 1. Lung infection with RSV was also associated with increased albumin in bronchoalvelar lavage fluid, a biomarker that distinguishes infection-induced lung injury from WPS-induced lung injury, Figure 2. Other biomarkers of inflammation (TNF-α and IL1β) and oxidative stress (SOD) increased in both types of injuries. In mice exposed to WPS and infected with RSV, the intensity of inflammatory infiltrates (mainly lymphocytes), the size of damage to the distal airway spaces and the size of involved area were clearly higher than in control mice. Despite the increased disease, lung viral load was not significantly affected by exposure to WPS.

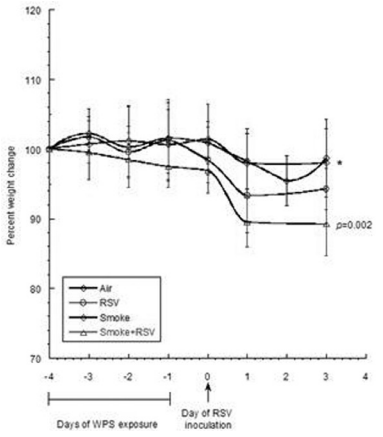


Figure 1. Body weight changes in mice following short-term nose-only water-pipe smoke or air (control) exposure with or without RSV infection. Data (mean ± SD) are percentages of daily weights divided by the starting weight for each condition. The shown $p$ value denotes comparison between (WPS exposed + RSV infected) and (Air exposed only) groups; * indicates the comparison group.

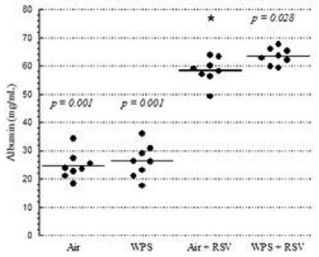


Figure 2. Concentrations of albumin in bronchoalveolar lavage fluid of mice following short-term nose-only water-pipe smoke or air (control) exposure, with or without RSV infection (day 3 post-infection). The shown $p$ values denote comparison between each indicated group and (Air exposed RSV infected) group; * indicates the comparison group.

***Conclusion.*** In this model, short-term water-pipe smoke exposure resulted in severe RSV disease (increased weight loss) and worsened pathology.

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

### 629. Blood Transcriptome Variations Predict Infection and Rejection in the Older Kidney Transplant Recipient

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**.** Compared with younger patients on similar immunosuppression regimens, older solid-organ transplant recipients experience increased rates of infection and death, but decreased rates of rejection. Our previous findings demonstrated increased T-cell immunosenescence and pro-inflammatory monocytes in older patients. This study sought to define the implications of transcriptome alterations for clinical outcomes. The objective of this abstract is to evaluate older vs. younger solid-organ transplant recipients for differential patterns of gene expression associated with infection and rejection.

***Methods.*** Peripheral blood mononuclear cells were isolated from 23 older (≥age 60) and 37 matched younger (ages 30–59) kidney transplant recipients at 3 months after transplantation. RNA extraction was performed on banked PBMCs. Isolated RNA was converted to fluorescent cRNA and hybridized to Illumina Human HT-12 v4 BeadArrays. Gene expression values were quantile-normalized and log2-transformed for mixed effect linear model analyses to identify differential expression as a function of age, adjusted for induction type, donor type, and sex. Statistical analysis was performed using R software.

***Results.*** Genes differentially expressed in older patients revealed an over-representation of pro-inflammatory genes and a down regulation of genes associated with the CD8 immune response. Patients who went on to develop infection demonstrated an increase in IRF transcription factor activation and plasmacytoid dendritic cell activity. Patients who developed rejection demonstrated an increase in myeloid lineage immune cell activity.

***Conclusion.*** Differential patterns of gene expression were observed in patients who developed infection in the first year after kidney transplantation. These findings were distinct from the gene expression changes associated with development of rejection. These findings may explain the mechanism behind vulnerability to infection in older transplant patients. In addition, monitoring of changes in gene expression may provide an avenue for patient monitoring after transplantation as well as individualization of immune suppression after solid-organ transplantation.

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