Methods: Fifteen pneumococcus strains expressing 14 different serotypes, including one non-encapsulated strain (R36Aa), were studied with flow cytometry (FC) and confocal fluorescence microscopy (CFM) for DBA binding. Pce enzyme activity was detected with a colorimetric assay using p-nitrophenyl-phosphorylcholine as the substrate. Mutant strains with pce knocked-out were constructed in R36A and D39 by replacing pce with Janus cassette. Both licD genes were sequenced for some of the strains.

Results: Ten of the 15 strains had Pce activity and all of them bound DBA (Table 1). When the pce gene was inactivated in two normally Pce-positive strains (R36Aa/pce and D39pce), the strains did not show DBA binding by CFM (Figure 1). Thus, expression of Pce appears to be sufficient for expressing the DBA antigen. Of the five strains that had no Pce activity, two bound DBA. Sequencing of the licD genes in these two strains with positive DBA binding and negative Pce activity revealed one SNP in licD1 and four SNPs in licD2, resulting in a single amino acid difference each for LicD1 and LicD2, compared with R36A and D39.

Conclusion: DBA can bind to the terminal α-GalNAc-(1→3)β-GalNAc of pneumococcal TA and LTA, which is created by Pce. DBA binding is independent of capsule type. The unexpected binding of DBA to the two Pce-negative strains suggests that there is a Pce-independent mechanism for generating the target for DBA binding. Since LicD1 and LicD2 are involved in attaching PC to a α-GalNAc-(1→3)β-GalNAc, we are now investigating their role in creating DBA targets independent of Pce.

Table 1. Summary of DBA binding (DBA +/−) by FC and CFM, and associated Pce enzyme activity (Pce +/−)

| DBA (+) | DBA (-) | Total |
|--------|--------|-------|
| Pce (+) | 10     | 0     | 10    |
| Pce (-) | 2      | 3     | 5     |
| Total   | 12     | 3     | 15    |

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2598. Macrophage Migration Inhibitory Factor May Contribute to Disseminated Coccidioidomycosis Susceptibility
Camila D. Odi, MD; Lin Leng, PhD; Edwin Su, MS; Marta Pieczyhna, MS; John N. Galgiani, MD; Steven M. Holland, MD; Richard Bucala, MD, PhD; Yale Department of Internal Medicine, New Haven, Connecticut; University of Arizona College of Medicine, Tucson, Arizona; Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

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Background: Disseminated coccidioidomycosis occurs in <1% of cases, and genetic polymorphisms may account for some of the variability in infection severity. Macrophage migration inhibitory factor (MIF) is an inflammatory cytokine with two promoter polymorphisms linked to variability in expression. High expression MIF polymorphism may be associated with granulomatous with polyangiitis (GPA), sarcoidosis and tuberculosis. Despite the overlap between MIF and Coccidioides immunity, MIF has never been studied in coccidioidomycosis.

Methods: A549 cells transfected with MIF promoter/luciferase plasmids of 0 or 8 CATT repeats were stimulated with 50 μg/mL of inactivated C. posadasi spherule lysate, and luciferase expression was measured as relative units (RU) of luminescence. Genomic DNA from patients with disseminated coccidioidomycosis (n = 37) and healthy controls (n = 371) was analyzed for the 794 CATT or microsatellite and the -173 C. SNP. Cohorts were divided into self-identified African Americans and Caucasians, and allele frequencies were compared using Fisher exact test. Plasma MIF levels were analyzed by enzyme-linked immunosorbent assay using specific antibodies, and levels were compared by T-test.

Results: Human lung epithelial cells exposed to Coccidioides spherules had significantly higher MIF expression than unexposed cells (3.94 ± 0.44 vs. 3.02 ± 0.24 RU, P = 0.0162). Among Caucasians (n = 26), the high MIF expression −173C containing genotype was present in 50% of the coccidioidomycosis patients vs. 40% of healthy controls (P = 0.396). The −794 CATT containing genotype was present in 40% of patients vs. 27% of controls (P = 0.240). Plasma MIF levels were higher in coccidioidomycosis patients with high- vs. low-expression alleles (P = 0.008), but lower in patients vs. controls (P = 0.0001)

Conclusion: Coccidioides spherules stimulated MIF expression in human lung epithelial cells supporting the hypothesis that MIF is involved in immunity against this pathogen. In Caucasian subjects, the higher MIF expression alleles were more common in patients with disseminated coccidioidomycosis when compared with healthy controls, although significance was limited by sample size. This is consistent with high expression MIF alleles associated with other granulomatous diseases, and may reflect destruction of the granuloma with pathogen dissemination.

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2599. Studying the Effects of Altering Histone Modification on Aspergillus fumigatus Virulence
Pam Lee, MD; Hong Liu, PhD; Scott Filler, MD; Harbor UCLA, Los Angeles, California

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Background: As there are few drugs for treating invasive aspergillosis, there is an urgent need for new antifungal agents. Enzymes involved in histone modification are possible antifungal drug targets. We set out to investigate whether genes whose products are involved in histone modifications influence the virulence of Aspergillus fumigatus (Af).

Methods: Genes whose products were likely involved in histone modification were deleted in strain Af293 using CRISPR-Cas9. Virulence was assessed in a triadial model of invasive pulmonary aspergillosis. The extent of Af-induced damage to the A549 pulmonary epithelial cell line was determined by Cr release assay.

Results: Af genes were selected for investigation based on their homology to genes encoding known histone modifying proteins and their high expression level in vivo. The genes were predicted to encode members of the COMPASS histone acetyltransferase complex (csla/cre2, afu5g06000), the SAGA histone acetyltransferase complex (spt3, spt8), and the RPD3 histone deacetylase complex (hosk). The Δcsla and Δspt8 mutants had significant growth defects on rich media and were not tested further. The Δspt3 and Δhosk mutants grew normally and had mild conidiation defects. The Δcre2 mutant had wild-type (WT) growth and conidiation in vitro. Mice infected with the WT strain had 100% mortality within 9 days whereas mice infected the Δspt3, Δspt8, and Δhosk mutants had only 40% mortality by 21 days. The Δhosk mutant also had impaired capacity to damage pulmonary epithelial cells in vitro.

Conclusion: Csc and Spt3, components of the COMPASS complex, are required for normal growth in vitro. Spt3 and Spt8, members of the SAGA complex, are required for normal conidiation and virulence. HoskA, part of the RPD3 complex, is necessary for maximal virulence and induction of host cell damage. Our results suggest that the HoskA histone deacetylase may be a promising drug target for treating invasive aspergillosis.

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2600. Mannose-Binding Lectin Polymorphisms Are Important Modulating Factors in Community- and Hospital-Acquired Pneumonia Caused by Legionella spp.
Povilas Kaulaviunas, MSC; Ruta Prakauskiene, MS; Frederic Saub, BSc; Ruta Petraitis, MD; Sophie Jarraud, PhD; Rasa Semokas, MSC; Rasa Baneviciene, MSC; Rita Planciuniene, PhD; Thomas J. Walsh, MD, PhD (hon); Vidmantas Petraitis, MD; Well Cornell Medicine of Cornell University, New York, New York; Institute of Infectious Diseases and Pathogenic Microbiology, Lithuania; University of Arizona College of Medicine, Tucson, Arizona; National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

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Background: Mannose-binding lectin (MBL) and its soluble receptors (sMBLs) are innate immune factors that activate the complement system and mediate phagocytosis of microorganisms. MBL, MASP-2 and MASP-3 are essential for the recognition and killing of L. pneumophila; therefore, polymorphisms in MBL and its sMBLs may affect the severity of L. pneumophila pneumonia. The -173 CATT repeats in the MBL gene promoter are associated with variable expression and disease susceptibility in other pathogen infections. A3G1 polymorphisms in the sMBLs are associated with resistance to H. capsulatum. Therefore, the aim of this study was to evaluate the association between MBL and sMBL -173 CATT repeat polymorphisms and the severity of L. pneumophila pneumonia.

Methods: We used a case-control study design to examine the association between MBL and sMBL -173 CATT repeat polymorphisms and the severity of L. pneumophila pneumonia in patients with hospital-acquired and community-acquired pneumonia. Genomic DNA from patients with hospital-acquired (n = 54) and community-acquired L. pneumophila pneumonia (n = 53) was used to genotype the -173 CATT repeat polymorphism in the MBL gene promoter. Patients with high-expression alleles had significantly more severe disease (P = 0.013, OR = 4.40) and increased mortality (P = 0.039, OR = 3.25) compared to patients with low-expression alleles.

Results: MBL and sMBL CATT repeat polymorphisms were associated with the severity of L. pneumophila pneumonia. Patients with high-expression alleles had significantly more severe disease and increased mortality compared to patients with low-expression alleles.

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Background: Although multiple different virulence factors have been identified for Staphylococcus aureus, there is limited information on genetic variation present between different strains of S. aureus in the clinical setting. To better define whether differing virulence factors could contribute to differing clinical manifestations of S. aureus infections we undertook a comparison of the frequency of virulence and antibiotic resistance genes present in S. aureus isolates from different clinical sites.

Methods: Whole-genome sequencing was performed on a convenience sample of S. aureus isolates from clinical or surveillance cultures obtained at an academic medical center over a 27-month period. Genomic assemblies were generated and annotated to define protein-coding regions. The prevalence of 28 genes previously defined as being associated with S. aureus virulence or antimicrobial resistance, including MSCRAMM genes, was then analyzed in relation to nine specific culture sources including only a single isolate from each culture source per patient using a likelihood ratio $\chi^2$ analysis.

Results: There were 1286 S. aureus isolates with draft assemblies and annotations, and there was a statistically significant $(P < 0.001)$ difference in gene frequencies between culture sources for 18 genes that included 13 of 19 virulence factors, 4 of 7 antibiotic resistance genes and 1 of 2 MSCRAMM genes. The most notable variation was seen for the presence of the sec, esp, efb, lukS, lukF, fnb, mecA, and emm5 genes (all with $P < 0.0001$). There were also significant variations in overall gene frequency patterns between isolates from wound, blood, and respiratory isolates $(P < 0.0001)$, as well as significant differences in the frequency of com and hyl genes between surveillance and clinical isolates $(P < 0.001)$.

Conclusion: This study demonstrates a difference in the prevalence of virulence and antibiotic resistance genes in S. aureus isolates based on the culture source. As the culture location can be considered a surrogate for different types of infections (such as bloodstream pneumonia, urinary tract infections) these differences in gene frequency may contribute to variation in the clinical manifestations of infections by differing S. aureus strains.

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2603. Biofilm Formation as a Predictive Marker of Prognosis for Escherichia coli Sepsis

Kailu Zhang, Bachelor of Science; Daniella Schneider, Masters Physician Assistant; Rakesh Biswas, Medical Degree (MD); Mariana Gomez de la Espriella, IM/Infectious disease; Jayasinha Rao, PhD; Anthony Baillie-Bonnie, Medical Degree (MD); Virginia Tech Carilion School of Medicine, Roanoke, Virginia; Virginia Tech Carilion Clinic, Virginia Tech, Blacksburg, Virginia; Virginia Tech School of Medicine, Carilion Clinic, Jefferson College of Health Sciences, Roanoke, Virginia; Carilion Clinic/VTCOMS, Roanoke, Virginia

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Background: Escherichia coli is the Gram-negative organism most commonly associated with bloodstream infections and death due to sepsis. Timely administration of appropriate antibiotics plays a significant role in improving patient outcomes. E. coli expresses virulence factors (VFs) such as biofilm formation and motility phenotypes which play a role in bacterial attachment and dissemination by enabling immune system evasion and host migration. The role of these VFs in bacteremia prognosis is not well characterized. Our study aims to evaluate the clinical characteristics and outcomes of E. coli bacteremia patients specifically in relation to biofilm forming isolates.

Methods: 91 E. coli bacteremia clinical isolates were consecutively collected from patients between 2013 to 2015. Virulence factor phenotypes were determined by in vitro biofilm formation, motility, and milk hydrolysis. Clinical patient data associated with the isolates were abstracted from the electronic medical records database and blinded from research team throughout characterization. Descriptive statistics were used for clinical variables and analyzed in a dichotomized fashion based on biofilm formation. The chi-square or Fisher exact test were used for categorical data and the Mann–Whitney U or Student T-test for continuous variables as appropriate.

Results: Of the 91 isolates, 41 had a biofilm-forming phenotype. Of the 87 isolates tested for milk hydrolysis and motility a positive finding was seen in 61 (70%) and 67 (77%) isolates, respectively. In the multivariate model, patients with E.coli bacteremia from biofilm producing isolates were at increased risk of death or going into hospice during that hospitalization. (OR,9.9; 95% CI, 1.1,88.7, P = 0.041)

Conclusion: Patients with biofilm-forming E. coli bacteremia had worse clinical outcomes than their non-biofilm forming counterparts suggesting that this phenotype leads to a more pathogenic organism. A prospective study to confirm this finding is needed as is the design of rapid diagnostics to promptly identify this phenotype in septic patients.