Conclusion. During the acute phase of infectious disease with severe inflammation, iron levels were immediately decreased due to enhanced production of hepcidin-25. Understanding of host iron status may be essential for effective use of siderophore cephalosporin, with a unique mechanism of action involving the use of bacterial iron uptake systems.

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637. B-Lactam (BL) Antibiotics Promote an IL-1β Response in Patients with Staphylococcus aureus Bacteremia (SaB)
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Background. BL therapy has been associated with reduced SaB duration compared with non-BL therapy. It has been shown that patients with SaB who fail to generate increased serum IL-1β at risk for prolonged SaB (>4 days duration), a predictor of mortality. This suggests a major role for the IL-1β host response in prompt clearance of SaB. Furthermore, BL resulted in reduced peptidoglycan cross-linking, reduced peptidoglycan O-acetylation, and increased alpha-toxin expression, all of which have independently been shown to enhance IL-1β release. This study aims to show that BL therapy results in a more robust IL-1β host response compared with non-BL therapy to explain, in part, more rapid SaB clearance.

Methods. Fifty-nine patients (47 MRSA and 12 MSSA) with diverse SaB sources, including endovascular, extravascular (e.g., pneumonia), and cather-related infections were included. In the first 48 hours, patients were treated with either BL, including oxacillin, or vancomycin or daptomycin (n = 35). BL-1β concentrations were determined by ELISA on serum samples obtained on Days 1, 3, and 7 after bacteremia onset and compared between groups by Mann–Whitney U-test.

Results. Patients in BL and non-BL groups had similar IL-1β concentrations on Day 1 of bacteremia (median BL 4.4 pg/mL vs. non-BL 2.8 pg/mL, P = 0.09). BL-treated patients had significantly higher IL-1β serum concentrations on Day 3 (median 7.54 mg/mL vs. 1.9 pg/mL; P = 0.007) and Day 7 (12.52 mg/mL vs. 1.56 pg/mL; P = 0.016) when compared with non-BL-treated patients. BL therapy resulted in 23% and 105% increase in IL-1β at Days 3 and 7, respectively, while non-BL treatment resulted in 32% and 44% reduction in IL-1β. The median duration of SaB was similar between BL and non-BL-treated patients (2.5 vs. 2.0 days, respectively, P = 0.59).

Conclusion. Given that a lack of inflammasome-mediated IL-1β production is associated with prolonged SaB, the significant increases in IL-1β levels in patients treated with BL has important therapeutic implications. Previously observed reduced duration of MRSA bacteremia with the addition of BL to vancomycin may have its basis on enhancing IL-1β release. A therapeutically relevant regimen of vancomycin or daptomycin in combination with BL to treat MRSA bacteremia and use of BL in MSSA bacteremia is promising to improve outcomes based on these results.

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638. CMV-Specific T-Cell Immune Responses in Older vs. Younger Kidney Transplant Recipients
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Background. 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. The mechanism behind these differences has yet to be defined, but may be related to OsmilagatingO driven by CMV infection. The objective of this study was to evaluate older vs. younger solid-organ transplant recipients for CMV-specific T-cell immune responses.

Methods. Peripheral blood mononuclear cells were isolated from 20 older († age 60) and 25 matched younger (ages 30–59) kidney transplant recipients at 3 months after transplantation. Eight recipients were at high risk by CMV serology (D+/R−) and 37 were intermediate risk (D−/R+). Overlapping CMV peptide pools were used for stimulation. Intracellular staining to determine cytokine stimulation was performed by multiparameter flow cytometry. Statistical analysis was performed using Jmp Pro 11 software.

Results. There was no association between patient age and CMV risk status (P = 0.728). There was no difference between older and younger kidney transplant recipients in release of IFNγ, TNFa, or IL-2 from CD4+ or CD8+ T cells in response to CMV antigen stimulation. However, Older recipients had similar frequencies of CD8+ naive cells but decreased frequency of CD8+ terminally differentiated effectors. Memory CD45RA− (TEMRA) T cells releasing both IFNγ and TNFa (P = 0.037) (figure). Interestingly, development of CMV viremia was associated with a weaker CMV-specific immune response: Patients who had a history of CMV viremia had a decreased frequency of CD8+ TEMRA cells releasing both IFNγ and TNFa (P = 0.041).

Conclusion. Older kidney transplant recipients demonstrated a decreased frequency of CMV-specific polyfunctional CD8+ TEMRA T cells. This impaired memory T-cell response to CMV suggests a possible mechanism for the increased vulnerability of older recipients to CMV infection or reactivation, which may in turn worsen age-related immune dysfunction. Furthermore, patients with subsequent CMV viremia had a decreased frequency of CMV-specific polyfunctional CD8+ TEMRA cells resulting in patient vulnerability to CMV viremia despite modern protocols for antiviral prophylaxis.

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639. Indoleamine 2,3 Dioxigenase, Age, and Chronic Immune Activation in HIV Patients
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Background. Immune activation complicates HIV despite antiretroviral therapy (ART). Indoleamine 2,3 dioxigenase (IDO) catabolizes tryptophan (T) to kynurenic (K), regulating immune activity. IDO activity increases in HIV patients and non-HIV patients with age. This study examines the relationship of IDO activity, bacterial translocation, and ageing in HIV patients on ART. We hypothesize that increased IDO activity caused by bacterial translocation is a factor in inflammation during aging.

Methods. Samples and data from virologically suppressed HIV patients on ART in specific age strata were obtained from the Centers for AIDS Research Network of Integrated Clinical Systems. Samples and data from age and sex-matched healthy controls were obtained from the Multicenter AIDS Cohort Study and the Women’s Interagency HIV Study. The ratio of K/T (K/T) and neopterin were used as indicators of inflammation; 16S ribosomal DNA (16S rDNA) and lipopolysaccharide (LPS) served as markers of bacterial translocation. Log transformation, chi-square tests, t-tests with Satterthwaite adjustment for continuous data, ANOVA, and ANCOVA homogeneity of slopes model were used.

Results. Samples and data from 205 HIV patients and 99 matched controls were analyzed. HIV patients had higher K/T values across all ages. Younger HIV patients had greater K/T values than older healthy controls. Age, sex or race was not associated with differences in K/T. Current CD4 count or CD4 nadir had no association with K/T ratio. For HIV patients, there was an inverse relationship between LPS detection and K/T. For controls, there was no association between LPS and K/T. There was no association between PCR detection of 16S rDNA and K/T ratio in HIV patients or controls. Both groups had positive association between K/T ratio and neopterin.

Conclusion. HIV patients have elevated K/T, even at younger ages, despite virologic control. The main hypothesis that K/T increases with advancing age was not supported in this cohort. Also, unlike other published literature, CD4 nadir, LPS, and 16S rDNA did not correlate with K/T ratio. This study suggests there may be an alternative driver of immune inflammation in well-controlled HIV patients other than bacterial translocation.

Figure 2. Age and K/T ratio.

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640. Prospective Association of Serum Vitamin D Level with Sepsis-Mortality in Postmenopausal Women: Results From the Women's Health Initiative

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Methods. This is a prospective study composed of participants from the Women’s Health Initiative (WHI) in the Vitamin D/Calcium trial who have been followed for an average of 15 years. The analysis sample consists of participants who had 25(OH)D measured at baseline. Patients with kidney disease and self-reported cancer at enrollment were excluded. Vitamin D deficiency was defined as levels ≥ 20 ng/mL which was categorized into severe deficiency [25(OH)D] 12 ng/mL and mild deficiency [25(OH) of 12–20 ng/mL]. Cox proportional hazard model was used to study the association between serum Vitamin D and sepsis mortality.

Results. 10,814 participants were included in the study (mean age = 64.4 years). At baseline, 49.26% (n = 5,328) of the sample had vitamin D deficiency and of those who died from sepsis, 57.7% (n = 41) where found to be vitamin D deficient. We found statistically significant increased hazard ratios (HR) for sepsis mortality in mild (HR = 1.19; 95% CI 1.00–1.41) and severe vitamin D deficiency (HR = 1.82; 95% CI 1.50–2.11) in age adjusted and fully adjusted models (Table 1).

Conclusion. Vitamin D deficiency is associated with increased risk of sepsis mortality in postmenopausal women, which was seen in all ages. A clinical trial evaluating adequate supplementation in patients with sepsis is recommended to assess clinical significance.

Table 1. Cox models for sepsis mortality (Hazard Ratio with 95% CI)

| Models | Continuous Vitamin D* | Severe Deficiency | Mild Deficiency | No deficiency |
|--------|-----------------------|------------------|-----------------|--------------|
| Model 1: Crude | 1.27 (1.17, 1.37) | 2.11 (1.36, 2.53) | 1.27 (1.08, 1.49) | (ref) |
| Model 2: Age-adjusted | 1.24 (1.15, 1.34) | 2.08 (1.23, 2.95) | 1.20 (1.02, 1.41) | (ref) |
| Model 3: Age + SEES** | 1.19 (1.10, 1.28) | 1.94 (1.61, 2.33) | 1.17 (0.99, 1.38) | (ref) |
| Model 4: Age + Behavioral variables*** | 1.20 (1.11, 1.31) | 1.49 (1.20, 1.85) | 1.15 (0.97, 1.35) | (ref) |
| Model 5: Fully adjusted | 1.19 (1.10, 1.30) | 1.92 (1.52, 2.40) | 1.19 (0.99, 1.40) | (ref) |

*Vitamin D levels ≤ 20 ng/mL are deficient. **SEES variables: education, income, marital status. ***Behavioral variables: smoking, daily exercise, alcohol intake, BMI, diet.

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641. Development of Structural Epitope Targeting During B-cell Ontogeny by Exploration of Relatives of gp41 Structural Epitope Binding Antibody 6F5

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Background. In previous studies, our lab has characterized a number of highly mutable antibodies against structural epitopes of the human immunodeficiency virus (HIV) envelope protein. These antibodies were first isolated from long-term nonprogressors (LTNP). We have previously mapped 6F5 to a novel structural epitope that encompasses areas in both heptad repeats of GP41, mapping to amino acids of 557, 654 and 657 of reference sequence HXB2. In these studies, three other antibodies that were ≥90% homologous to 6F5 also resolved amino acid 657. On sequence analysis, 6F5 and its relatives had the same gene usage and general structure. These similarities and the similar epitope mapping implied these were once distantly related to a single B-cell lineage. As fusion of the viral membrane to the target cell depends on these heptad repeat regions associating and forming a six-helix postfusion bundle, antibodies that can interfere in this may be highly useful.

Methods. See results.

Results. Because 6F5 maps to 557 and 654/657 which are widely separated on the HIV) envelope protein. These antibodies were first isolated from long-term nonprogressors (LTNP). Antibodies that compete 6F11 are much more prevalent in LTNP than normal progressors (75% vs. 20%). Functionally, we found that despite being mapped to a similar portion of GP41 (657), only 6F5 is shown to have significant ADCC activity, however relative 6F11 does not.

Conclusion. If targeting these epitopes correlates with the LTNP state, then these sites may be highly significant as targets of therapeutics or in vaccine strategies. Further studies on a larger cohort of LTNP are ongoing. Additionally, deep sequencing of antibody sequences are being done to explore the development of structural epitope targeting by this family of antibodies.

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642. B- and T-Cell Responses to Pneumococcal Polysaccharide and Protein Vaccine Antigens in Recently Diagnosed HIV-1-Infected Patients

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Background. Prevention of serious HIV-1-associated pneumococcal infections may be optimized by the limited magnitude and function of vaccine-induced antibodies. Responses to the T-independent pneumococcal capsular polysaccharide (PPS) + T-dependent diphtheria toxoid (DT) protein conjugate vaccine (PCV-13) may be influenced by CD4+ T follicular helper (TFH) cells which provide specific help for B-cell differentiation.

Methods. We immunized 22 control and 19 newly diagnosed HIV-1-infected adults (median 610 CD4+ T-cells/μL; range: 139–1,408) and 69,316 plasma HIV RNA (range 232–806,936) on ART for 1–4 months with PCV13. We measured (i) PPS-specific antibody-secreting cells (ASCs) by ELISPOT on Weeks 0 and 1, (ii) serum IgG to 11 PPS serotypes (SRP) by multiplex ELISAs on Weeks 3 and 12, and (iii) titers of opsonophagocytosis (OP) for four STs at Weeks 0 and 8, and (iv) numbers and activation (ICS expression) of circulating TFH cells by flow cytometry on Weeks 0 and 1. Values were compared by ANOVA, paired and unpaired t and Mann–Whitney tests.

Results. The number of PPS-specific IgG, IgM and IgA ASC increased significantly from Weeks 0 to 1 post-PCV13 and to similar magnitude in both Controls and HIV+ subjects, returning to baseline by Week 8. Levels of serum PPS-specific IgG increased significantly from Weeks 0 to 8 for 10/11 STs, 7/11 STs in Controls and HIV+ subjects, respectively, (P<.05) and to comparable levels. Similarly, OP titers increased significantly and similarly to each of four STs in both groups from Weeks 0 to 8. In contrast, although DT-specific IgG ASC increased from Weeks 0 to 1 in HIV+ and controls, these values were lower among HIV+1 adults (P=.001). Consistent with these limited responses, a key regulatory molecule on THF cells, elicited largely by T-dependent antigens (DT), was upregulated on cells from Control but not HIV+ at Week 1. Moreover, levels of IL-12, which drives TFH differentiation, were also lower among HIV+1 at Week 1.

Conclusion. Humoral responses to PPS are largely intact (ASC, serum IgG2 and killing function) with recently diagnosed HIV-1 infection, highlighting the importance of HIV+ recognition. The DT and TFH activation to vaccine responses are more limited, even with high CD4+ counts and ART, suggests a more rapid and perhaps more recalcitrant HIV-1-associated T-cell defect.

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643. Coronary Artery Aneurysms Are Found on Blindly Read Echocardiograms From Febrile Patients with and without Kawasaki Disease

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Background. In 2017, the American Heart Association published new Kawasaki disease (KD) guidelines including echocardiographic (echo) criteria for diagnosis of incomplete KD (iKD). Echo is positive if ≥ 1 or more coronary arteries (CA) show aneurysmal dilation (Z-score of ≥2.5) or if a CA has milder dilation (Z-score of 2–2.49) plus ≥2 of the following: decreased left ventricular function, mitral regurgitation, and pericardial effusion. While CA dilation is seen commonly in KD and iKD, specificity of this finding is unclear because patients with systemic febrile illnesses may have CA dilation. To assess specificity of the American Heart Association criteria, blinded readers measured CA dimension in patients with KD and iKD and in febrile and healthy patient controls.

Methods. This is a single-center retrospective study. De-identified echo clips of CA from patients age 0–10 years were interpreted blindly and independently by six pediatric cardiologists. KD and iKD diagnoses were based on clinical data and IVG treatment. Control groups were healthy patients evaluated for a benign murmur and febrile patients with fever ≥272 hours without a KD diagnosis or IVG treatment. Detection of left ventricular dysfunction, mitral regurgitation and effusion was recorded. An echo was considered positive if the reading from at least one reader met AHA criteria for KD.