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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Backgrounds. Vitamin D deficiency has been studied in the critically ill, and has been associated with worse morbidity and mortality rates, especially in those admitted with sepsis. Sepsis is a major cause of ICU admissions and accounts for 250,000 deaths per year. Dihydroxyvitamin D can inhibit the production of interleukins, tumor necrosis factor and can also increase the expression of endogenous antimicrobial peptides. This study sought to assess if low serum concentrations of 25(OH)D were associated with higher sepsis mortality rates.

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 ² 20 ng/mL, which was categorized into severe deficiency [25(OH)D ²12 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: 1.50–2.21) 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 (Hazards Ratio with 95% CI)

Models	Continuous Vitamin D*	Vitamin D Level		
		Severe deficiency	*Mild deficiency*	*No deficiency*
Model 1: Crude	1.27 (1.17, 1.37)	2.11 (1.76, 2.53)	1.27 (1.08, 1.49)	(ref)
Model 2: Age-adjusted	1.24 (1.15, 1.34)	2.08 (1.73, 2.49)	1.20 (1.02, 1.41)	(ref)
Model 3: Age + SES**	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)	1.79 (1.48, 2.18)	1.15 (0.97, 1.35)	(ref)
Model 5: Fully adjusted	1.19 (1.10, 1.30)	1.82 (1.50, 2.21)	1.19 (1.00, 1.41)	(ref)

* Vitamin D levels per SD decrease
** SES variables: race/ethnicity, education, income, marital status
*** Behavioral variables: smoking, daily exercise, alcohol intake, BMI, diet.

Fully adjusted: age, race/ethnicity, education, income, marital status, smoking, daily exercise, alcohol intake, BMI, AHEI

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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 mutated antibodies against structural epitopes of the human immunodeficiency virus (HIV) envelope protein. These antibodies were first isolated from long-term nonprogressors (LTNPs). We have previous 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 primary sequence, we explored if there was differential binding to the postfusion six-helix-bundle form. Two peptides (N36 and C34) each containing one of the heptad repeats can form the post-fusion six-helix-bundle *in vitro*. On sandwich ELISA testing, 6F11 and 7B6 did not bind any form. Interestingly, 4E4 specifically captured both peptides alone, but not the six-helix-bundle and 6F5 only bound the six-helix-bundle but not the other peptide.

A small number of samples were obtained to assess the prevalence of these responses in LTNPs. Antibodies that compete 6F11 are much more prevalent in LTNPs 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 LTNPs 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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Backgrounds. Prevention of serious HIV-1-associated pneumococcal infections may be compromised 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 (ASC) by ELISPOT at Weeks 0 and 1, (ii) serum IgG to 11 PPS serotypes (ST) by multiplex ELISA and (iii) titers of opsonophagocytosis (OP) for four STs at Weeks 0 and 8, and (iv) numbers and activation (ICOS expression) of circulating TFH cells by flow cytometry at 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 vs. 7/11 ST in controls and HIV+ subjects, respectively (P = NS), 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 TFH 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 IgG and killing function) with recently diagnosed HIV-1 infection, highlighting the importance of early HIV-1 recognition. That responses to T-dependent DT and TFH activation 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 IVIG treatment. Control groups were healthy patients evaluated for a benign murmur and febrile patients with fever ≥72 hours without a KD diagnosis or IVIG 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 iKD.

Results. Echos from 29 KD, 30 iKD, 28 febrile, and 27 healthy patients were reviewed. The initial echo of 41% of KD and 43% of iKD groups met echo criteria for diagnosis of iKD and 55% and 57%, respectively, had CA dilation or aneurysm. Among febrile patients, 7 (25%) had an abnormal CA size of which 4 (14%) met echo criteria for iKD. In the healthy patients, four (15%) had abnormal CA of which two (7.4%) met echo criteria for iKD. Among patients with a positive echo read, the median number of readers who read a CA as dilated was similar for each group. Furthermore, of all patients meeting echo criteria for iKD, 90% had aneurysmal CA dilatation.

Conclusion. Although CA abnormalities diagnostic of KD were commonly present at time of diagnosis in patients with KD or iKD, these findings were also present in some healthy and some febrile patients. Diagnosis of iKD in febrile children using echo criteria may result in an over-diagnosis of KD.

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644. How Antibody Isotype Affects Anti-Capsular Antibody Protection Against Carbapenem-Resistant *Klebsiella pneumoniae* Infection

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Background. New monoclonal antibodies (mAb) are being developed against infectious disease. However, antibody isotype is an important consideration, as different IgG variants interact with different Fc receptors and differ in avidity due to Fc structural differences. Our recent anti-capsular murine IgG_3 mAb 17H12 was shown to mediate protection against clade 2 ST258 carbapenem-resistant *Klebsiella pneumoniae* (CR-*Kp*). However, our previous studies showed an IgG_1 mAb to perform better than an IgG_3 mAb in mediating infection against a carbapenem-sensitive *Kp* isolate. Therefore, we sought to determine whether differences in antibody isotype contribute to differences in protection against CR-*Kp* infections.

Methods. We treated IgG_3-producing 17H12 parent hybridomas with LPS and IL-4 to generate isotype variants which were subcloned by sib selection. This yielded an IgG_1-producing clone which was sequenced and compared with the complementary-determining region (CDR) sequence of the parent. We then compared binding kinetics of the two mAbs to CR-*Kp* capsular polysaccharide by ELISA. Opsonophagocytosis by macrophages was compared between CR-*Kp* strains pre-opsonized with the IgG_1 or IgG_3 mAb. Finally, mice were infected intratracheally with CR-*Kp* pre-opsonized with either IgG_1 or IgG_3 mAbs and organ burdens were compared after 24 hours.

Results. Sequence analysis showed the IgG_1 antibody sequence to be identical to the 17H12 IgG_3 parent. Interestingly, the IgG_1 antibody bound at nanomolar affinity, but 10-fold less than the parent, suggesting loss of affinity or avidity. IgG_1-opsonized CR-*Kp* were phagocytized by macrophages 40–60% less than IgG_3-opsonized CR-*Kp*. However, both antibodies performed comparatively *in vivo*, reducing bacterial burden in the lung, liver and spleen of intratracheally infected mice by an average of 3 log.

Conclusion. The IgG_1 isotype variant of mAb 17H12 appears to have inferior binding and *in vitro* efficacy when compared with its IgG_3 parent, despite having the same CDR region. However, *in vivo* efficacy is unaffected in our model. Future studies plan to further analyze the differences in binding kinetics between these two antibodies, as well as their ability to bind pro and anti-inflammatory Fc Receptors and mediate the host response to CR-*Kp* infection.

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645. Mucosal-Associated Invariant T cells in Renal Tissue From Patients With Recurrent Urinary Tract Infections

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Background. Mucosal associated invariant T (MAIT) cells are innate-like T-cells involved in the antibacterial and fungal response by recognizing riboflavin metabolites produced by these organisms. MAIT cells are present in blood and are highly abundant in the mucosa of the liver, lungs and intestines. In murine models of urinary tract infection (UTI), MAIT cells appear to migrate to the bladder and decrease the bacterial load. It is however unknown whether MAIT cells reside in the human urogenital tract and renal tissue and whether they play a role in the first-line defense against (recurrent) UTI (RUTI).

Methods. We used a fluorescently labelled MR1-tetramer in conjunction with 14-color flowcytometry to identify and characterize MAIT cells in renal allografts after allograft failure caused by RUTI ($n = 6$) or rejection ($n = 6$) and in healthy kidney tissue surgically removed because of renal cell carcinoma (adjacent nontumorous tissue) ($n = 5$).

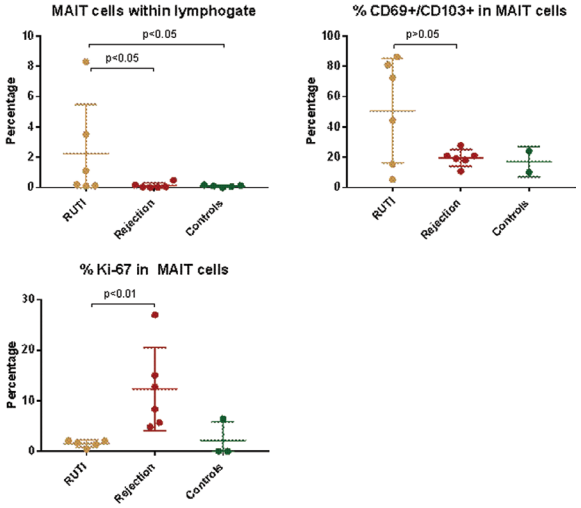
Results. The mean percentage of MAIT cells within the lymphogate was higher in the RUTI kidneys (2.24%) compared with the rejection kidneys (0.14%) and the control kidneys (0.11%) ($P < 0.05$).

Characterization of MAIT cells was impossible in some control samples due to MAIT cells counts <25 (predefined cutoff value), therefore the control group was excluded from further statistical analysis.

MAIT cells in RUTI kidneys appear to have a less activated profile compared with the rejection kidneys, with a lower expression of Ki67 ($P < 0.01$). Though the expression of the tissue resident marker CD69/CD103 was higher in 4/6 RUTI kidneys, this difference was not significant.

Conclusion. MAIT cells are present in renal tissue that is or has been subjected to an immunologic response. MAIT cells in RUTI kidneys display a more quiescent and in some samples more tissue resident phenotype than MAIT cells in rejection kidneys. These findings may suggest that (I) MAIT cells play a role in the first-line defense in the kidney and (II) that after RUTI, MAIT cells remain in renal tissue in a quiescent state. We postulate that this might be favorable in case of a second hit from an uropathogen.

Figure 1. Presence and characterization of MAIT cells in renal tissue.



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646. Activated Macrophages as Pathogenesis Factors in Ebola Virus Disease in Humans

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Background. Ebola virus disease (EVD) is associated with elevated cytokine levels that are more pronounced in fatal cases. This type of hyperinflammatory state is reminiscent of other inflammatory disorders, such as macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH). These are both part of a spectrum of rheumatologic phenomena characterized by both macrophage and T-cell activation. These disorders can be secondary to infection, malignancy, underlying rheumatologic disorder, or, paradoxically, immune deficiency.

Methods. Two cohorts of EVD patients were evaluated with respect to common plasma markers of HLH/MAS. Immunohistochemistry was used to evaluate tissue macrophages and viral antigens in various tissues from fatal cases of EVD.

Results. Neither fibrinogen nor soluble IL-2 receptor were significantly different between fatal and nonfatal cases. However, elevated levels of triglycerides, ferritin and sCD163, a marker of macrophage activation were noted in patients with EVD and they correlated with disease severity and a fatal outcome. Furthermore, significant immunoreactivity for CD163 + cells in host tissues was observed in fatal cases, predominantly in areas of extensive immunostaining for EBOV antigens.

Conclusion. These data suggest that host macrophage activation contributes to EVD pathogenesis and that directed anti-inflammatory therapies could be beneficial in the treatment of EVD.

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647. Characterization and Development of Human Monoclonal Antibodies to Pneumococcal Serotype 3

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