640. Prospective Association of Serum Vitamin D Level with Sepsis-Mortality in Postmenopausal Women: Results From the Women's Health Initiative Paulette Pinargini, MD; Reema Qureshi, MD; Wilmer Salazar, MD; Mary Roberts, MS; Charles Eaton, MD, MS; Linda Snetseelaar, PhD, RDN, LD; Meryl LeBoff, MD; Joseph Ann Manson, MD, MPH; Ikuko Kato, PhD and Erin S LeBlanc, MD, MPH.

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)D 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% (= 5,328) of the sample had vitamin D deficiency and of those who died from sepsis, 57.7% (= 41) where found to be vitamin D deficient. We found statistically significant increased hazard ratios (HR) for sepsis mortality in mild (HR ≥ 1.9; 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.

641. Development of Structural Epitope Targeting During B-cell Ontogeny by Exploration of Relatives of Gp41 Structural Epitope Binding Antibody 6F5 Sarah Baran, BA; Hakimuddin Sojar, PhD; Jonathan Hoffman, BA and Mark Hibar, MD, PhD; Pediatrics, University at Buffalo, Buffalo, New York

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. 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 KD.
Presence and characterization of MAIT cells in renal tissue.

Results. Echocardiograms 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 dilatation 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 echocardiogram, a 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, mAb 17H12 was shown to mediate protection against clade 2 ST235 carbapenem-resistant Klebsiella pneumoniae (CR-Kp). However, our previous studies showed an IgG, mAb to perform better than an IgG, 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-, producing 17H12 parent hybridomas with LPS and IL-4 to generate isotype variants which were subcloned by sib selection. This yielded an IgG, producing clone which was sequenced and compared with the complementarity-determining region (CDR) sequence of the parent. We then compared binding kinetics of the two mAbs to CR-Kp capsular polysaccharide by ELISA. Opsposphagocytosis by macrophages was compared between CR-Kp strains pre-opsonized with the IgG, or IgG, mAb. Finally, mice were infected intratracheally with CR-Kp pre-opsonized with either IgG, or IgG, mAbs and organ burdens were compared after 24 hours.

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

Conclusion. The IgG, isotype variant of mAb 17H12 appears to have inferior binding and in vitro efficacy when compared with its IgG, 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 FACS to identify and characterize MAIT cells in renal tissue. MAIT cells that did not adhere to the bladder were pre-opsonized with the bacterial load. To rule out an 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 (defined 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 immune 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.

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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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