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December 2018

PEDIATRIC RESEARCH ALLIANCE

Center for Childhood Infections & Vaccines

2018 CCIV Symposium Recap

The 2018 CCIV Symposium hosted two keynote speakers, five faculty talks, two pilot grant summaries, and ten posters. Attendance was good (but will be even better next year!) and there was animated discussion at the poster session and reception. Our keynote speakers were Latania Logan, MD, MSc from Rush University and Mathias Lichterfeld, MD, PhD from Harvard Medical School. Dr. Logan's Keynote was titled, "The Game of Hopscotch: Common to Plasmids, Antibiotic Resistance, and Kids." Dr. Logan, Chief of Pediatric Infectious Diseases at Rush, provided her perspective and research on the origins and consequences of multidrug resistant bacterial infections in children. In particular, her focus on regional differences in acquisition of multidrug resistant organisms is unique. One example she shared was the variability in rates of fluoroquinolone resistant Enterobacteriaceae diagnosed at three different children's hospitals in Chicago, where residence area was more strongly associated with infection than were traditional risk factors (antibiotic use, comorbidities, use of invasive devices, etc.). More research is certainly needed in this area given the continuing increase in infections caused by multidrug resistant microbes. Dr. Lichterfeld is a practicing adult infectious diseases physician and research leader in the immunopathogenesis of HIV, in particular the immunologic complexity of HIV-1 persistence during suppressive antiretroviral therapy. Dr. Lichterfeld's keynote was titled, "HIV-1 Reservoirs in Adults and Neonates" and he focused his remarks on an ongoing clinical trial in Botswana of very early treatment of HIV-1-infected infants. This NIH/NIAID-funded study was conceived and implemented following the report of the "Mississippi Baby" in 2013, who was infected with HIV-1 in utero and subsequently experienced over two years of HIV-1 remission after starting antiretroviral therapy at just 30 hours of life. Dr. Lichterfeld has established a cohort of very early treated infants that is providing an enhanced understanding of HIV-1-specific immune responses and HIV-1 reservoirs in infants. As the "Mississippi Baby" eventually demonstrated rebound of viremia, making it clear that very early treatment alone is likely not sufficient to cure HIV-1, Dr. Lichterfeld's cohort will soon receive novel interventions aimed at reducing HIV-1 reservoirs even further with the goal of a sustained remission in absence of daily therapy. This would be a major advance in the field and has the potential to benefit thousands of children infected with HIV each year.

The five faculty talks were given by Evan Anderson, MD, Lilly Immergluck, MD, MSCR, FAAP, Jens Wrammert PhD, Mehul Suthar PhD, and Stefan Sarafianos, PhD. In the first session of the afternoon, we learned about the incredible work taking place in the Vaccine and Treatment Evaluation Unit (VTEU) from Dr. Anderson and a novel geo-spatial approach to assess risk for community acquired methicillin-resistant *Staphylococcus Aureus* (CA-MRSA) from Dr. Immergluck. In the second session of the afternoon, we dived into humoral immunity against cholera with Dr. Wrammert, the Zika virus:placental interface with Dr. Suthar, and novel approaches to create antiviral drugs from Dr. Sarafianos. Last, but not least, the 2018 CCIV Symposium gave the CCIV Pilot Grant awardees, Inci Yildirim, MD, PhD, and Karen Kirby, PhD, the opportunity to give rapid fire talks on their funded projects. We look forward to their work on pneumococcal immunization in hematopoietic stem cell transplant recipients (Dr. Yildirim) and targeting the Enterovirus 71 RNA-dependent RNA polymerase (Dr. Kirby). In sum, the 2018 CCIV Symposium was a resounding success and we can't wait to do it again next year!

Check out photos from the symposium online and on page 5 of this newsletter.

—Ann Chahroudi, MD, PhD
CCIV Director

Inside this issue:

Ann Chahroudi

Recent Publication Highlights

View all recent publications on CCIV's website or click here.

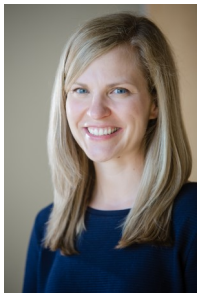
Clinical Features and Outcomes of Immunocompromised Children Hospitalized With Laboratory-Confirmed Influenza in the United States, 2011-2015..

Collins JP, Campbell AP, Openo K, Farley MM, Cummings CN, Kirley PD, Herlihy R, Yousey-Hindes K, Monroe ML, Ladisky M, Lynfield R, Baumbach J, Spina N, Bennett N, Billing L, Thomas A, Schaffner W, Price A, Garg S, Anderson EJ. J Pediatric Infect Dis Soc. 2018 Oct 25. PubMed PMID: 30358877.

Influenza is a common cause of respiratory tract illness in children and results in hospitalization in up to 1 per 1,000 children <5 years of age. Risk factors for hospitalization include younger age and other co-morbidities. The clinical characteristics and outcomes of influenza in immunocompromised children have not been well described. We used data from a US surveillance network of influenza hospitalizations during four recent influenza seasons to compare the clinical features and outcomes between children with and without immunocompromising conditions. Approximately 5% of the children in our study had an immunocompromising condition; the most common of these conditions included taking immunosuppressant medications (other than steroids), cancer, and having received a solid organ transplant (e.g., kidney, liver). We found that in both immunocompromised and non-immunocompromised children that the use of influenza vaccination (58% vs 39%, respectively) and the use of influenza antivirals within 48 hours of onset of symptoms (35% vs 27%, respectively) could be improved. We also found that although immunocompromised children had a longer duration of hospitalization, they were less commonly admitted to an intensive care unit than children without immunocompromising conditions. This unexpected finding may be related to an admission bias for immunocompromised children among medical providers.

-Submitted by the authors, please find the article here: www.ncbi.nlm.nih.gov/pubmed/30358877

Jennifer Collins was a pediatric ID fellow at Emory from 2014 – 2017 and is currently completing the two-year Epidemic Intelligence Service program at CDC.



Jennifer Collins

Visitor restriction policies and practices in children's hospitals in North America: results of an Emerging Infections Network Survey.

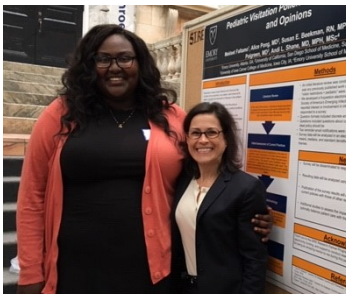
Pong AL, Beekmann SE, Faltamo MM, Polgreen PM, Shane AL. Infect Control Hosp Epidemiol. 2018 Aug;39(8):968-971. PubMed PMID: 29925447.

Like all innovative research, this study was designed over a cup of coffee with colleagues. Furthermore, it incorporated the talents of an undergraduate student enrolled in the Emory Undergraduate Research Program. We sought to understand how different hospital systems restrict patient visitation by friends and family during respiratory viral season when influenza, RSV, and other pathogens are circulating in the community. Visitor restrictions are designed to reduce the introduction of pathogens into the healthcare setting by family members and visitors. There is little evidence that visitor restriction policies accomplish this goal. Furthermore, there is notable heterogeneity among the timing of, indications for, and assessment of visitor restriction policies and practices (VRPP) in pediatric facilities. The Infectious Diseases Society of America Emerging Infections Network surveyed 334 pediatric infectious disease consultants via an electronic link. Descriptive analyses were performed. One hundred and 70 eligible respondents completed a survey between 12 July and August 15, 2016, for a 51% response rate. Of the 104 respondents (61%) were familiar with their VRPP, 92 (88%) had VRPP in all inpatient units. The respondents reported age-based VRPP (74%) symptom-based VRPP (97%), and outbreak-specific VRPP (75%). Symptom-based VRPP were reported to be seasonal by

Continued on page 3

Pong et al. continued

24% of respondents and to be implemented year-round according to 70% of respondents. According to the respondents, communication of VRPP to families occurred at admission (87%) and through signage in care areas (64%), while communication of VRPP to staff occurred by email (77%), by meetings (55%), and by signage in staff-only areas (49%). Respondents reported that enforcement of VRPP was the responsibility of nursing (80%), registration clerks (58%), unit clerks (53%), the infection prevention team (31%), or clinicians 16 (16%). They also reported that the effectiveness of VRPP was assessed through active surveillance of hospital acquired respiratory infections (62%), through active surveillance of healthcare worker exposures (28%) and through patient/family satisfaction assessments (29). This survey affirmed that visitor restriction policies and practices vary in scope, implementation, enforcement, and physician awareness in pediatric facilities. We recommend that a prospective multisite evaluation of outcomes of VRPP would facilitate the adoption of uniform guidance.

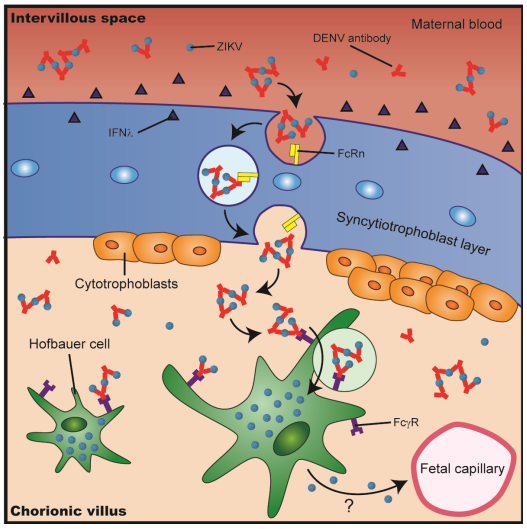


Mekleet Faltama, Emory College 2016 and Andi Shane at SURE poster presentation

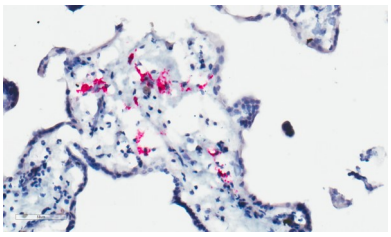
-Submitted by the authors, please find the article here: www.ncbi.nlm.nih.gov/pubmed/29925447

Cross-Reactive Dengue Virus Antibodies Augment Zika Virus Infection of Human Placental Macrophages.

Zimmerman MG, Quicke KM, O'Neal JT, Arora N, Machiah D, Priyamvada L, Kauffman RC, Register E, Adekunle O, Swieboda D, Johnson EL, Cordes S, Haddad L, Chakraborty R, Coyne CB, Wrammert J, Suthar MS. Cell Host Microbe. 2018 Nov 14;24(5):731-742.e6 . PubMed PMID: 30439342.



Since its introduction to the Americas in 2015, Zika virus (ZIKV), a single-stranded RNA flavivirus, has been responsible for the recent epidemic of neonatal neurologic defects. Previous work from our group identified fetal-derived placental macrophages (Hofbauer cells [HCs]) as permissive target cells of ZIKV infection within the placenta. Moreover, in collaboration with the Wrammert group, we found that antibodies to a closely related flavivirus, Dengue virus (DENV), can bind to ZIKV. It remains unclear how ZIKV crosses the placenta and how these cross-reactive antibodies facilitate vertical transmission of ZIKV. Here, we found that the presence of DENV antibodies increased the percentage of ZIKV-infected HCs from 10% to over 80% and subverted antiviral responses and interferon secretion in HCs, both of which are critical for clearance of virus. Using a mid-gestation human villous explant model system, we showed that enhancement of ZIKV infection is IgG-subclass dependent and that ZIKV immune complexes specifically target HCs within the villous stroma. We also discovered that these immune complexes can utilize the neonatal Fc receptor to facilitate transport of ZIKV across the placental barrier. Our findings emphasize the need for further understanding of flavivirus infection during pregnancy and its potential role in placental dysregulation and abnormal fetal development.



-Submitted by the authors, with images from the publication, please find the article here: www.ncbi.nlm.nih.gov/pubmed/30439342

Faculty Profile: Maud Mavigner, PhD

Maud Mavigner, PhD, is an Instructor, Research track in the Division of Pediatric Infectious Diseases at the Emory University School of Medicine since December 2016. She is also the Director of the CFAR Viral Reservoir core. After receiving her PhD in Immunology and Infectious Diseases in France (Université Paul Sabatier, Toulouse), Dr. Mavigner completed two postdoctoral fellowships at Yerkes National Primate Research Center and in the Department of Pediatrics of Emory.

Her postdoctoral research focused on developing strategies to cure HIV infection using the model of SIV/SHIV infection of rhesus macaques. Under the direction of Guido Silvestri, MD, she described the effect of hematopoietic stem cell transplant on the viral reservoir of ART-treated, SHIV infected rhesus macaques. Since 2013, under the direction of Ann Chahroudi, MD, PhD, she has completed multiple *in vivo* studies using nonhuman primates: (i) establishing a pediatric model of ART treatment of SIV infection in infant rhesus macaques; (ii) assessing the long term neurological consequences of Zika virus postnatal infection in rhesus macaque infants; (iii) targeting SIV reservoirs by combining early ART initiation and an innovative treatment inhibiting long-lived memory CD4+ T-cell renewal using a beta-catenin inhibitor, initially developed for cancer stem cell treatment. She also optimized ex vivo assays aimed at measuring the viral reservoir specifically in the SIV/rhesus macaque model, leading to the opening of a CFAR viral reservoir Core.

Dr. Mavigner is now pursuing her research targeting stem cell properties of memory CD4+ T-cells to reduce HIV persistence. She is also working at gaining a better understanding of HIV persistence in infants by assessing specifically the role of the naïve CD4+ T-cells.

Outside of the lab, Dr. Mavigner enjoys live music and cooking for her family and friends.

-Submitted by Maud Mavigner, PhD

Faculty Profile: Erica Johnson, PhD

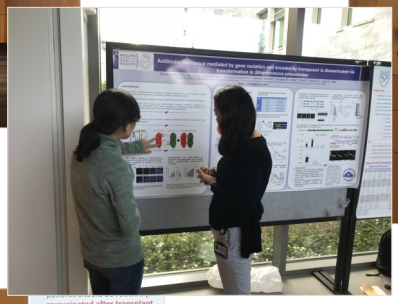
Erica Johnson PhD is a Junior Faculty Member in the Department of Pediatrics – Division of Infectious Diseases. Erica received extensive training in immunology and virology during her graduate studies at Morehouse School of Medicine and as a postdoctoral fellow in the Department of Pediatrics at Emory in the laboratory of Rana Chakraborty MD, PhD. Erica is dedicated to the field of pediatric infectious diseases and has a strong desire to make significant contributions leading towards a cure to end the HIV/AIDS epidemic in children, along with other clinically relevant pathogens that threaten a healthy start for children globally.

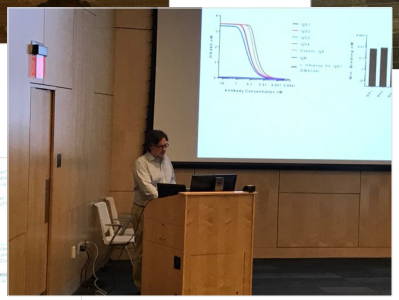
Erica's research has advanced the understanding of innate protection against MTCT of HIV-1 and pediatric immune responses to maternal viral infections. Understanding correlates of protection and mechanisms of natural immune control and how these can be exploited to develop interventions that limit viral infection during gestation are important to establish. Erica is particularly interested in placental and fetal immunology as it relates to HIV infection and plan to define mechanisms of protection and transmission during her career to further our understanding of HIV pathogenesis and vaccine development. Through novel ideas and excellent collaborations, this group has extensively characterized and published on viral infection (HIV-1, human cytomegalovirus [HCMV] and Zika Virus) and the innate immune responses of primary cells at the maternal-fetal interface. Erica's current research goals are to (1) define the dynamics of innate immune signaling in macrophages at the maternal-fetal interface and their control of HIV and HCMV during pregnancy; (2) determine the mechanisms by which HCMV exposure promotes in utero HIV transmission; and (3) Elucidate the impact of maternal infection and/or inflammation on the developing fetal immune system. This year, Erica was awarded a CFAR-R03 by the Emory CFAR for, "The Impact of Maternal Human Cytomegalovirus During Pregnancy on MTCT of HIV and Fetal Immunity." Through this mechanism, she hopes to generate novel pilot data for future NIH proposals.

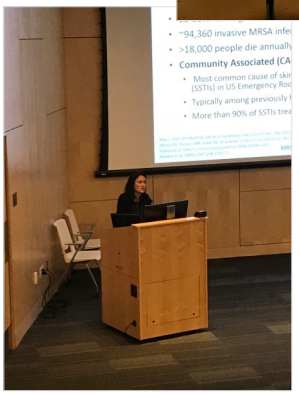
Outside of the laboratory, Erica enjoy reading, serving the community, and spending as much time as possible with her amazing husband Ira, and her beautiful and lively children, Ariyana (11) and David (15 months).

-Submitted by Erica Johnson, PhD

3rd Annual CCIV Symposium Photos







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The CCIV website is part of www.pedsresearch.org!

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Upcoming Events

CCIV Monday Morning Seminar

Spring 2019 schedule is available at our website: www.pedsresearch.org/research/centers/cciv

- December 24, December 31, January 7: Cancelled for Winter Break
- January 14: January 14: Samadhan Jadhao (L. Anderson Lab)
- January 21: Cancelled for MLK Jr. Day
- January 28: Maud Mavigner (Chahroudi Lab)
- See website for February through May schedule

Save the Date

CCIV is hosting Betsy Herold, MD of Albert Einstein College of Medicine for Egleston Grand Rounds on April 17, 2019. Check the website calendar for more details as the date approaches.

Archive

To see our newsletter archive, check out:
http://www.pedsresearch.org/research/centers/cciv/newsletters/

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