Editorial

Focusing on the Host Side of Host–Pathogen Interactions

Ravi Jhaveri, MD

The discipline of infectious diseases studies the interactions between hosts and pathogens.[1] Our field tends to focus most of our attention on the pathogens, but host susceptibility and protective factors play an important role in determining good or bad outcomes. *Staphylococcus aureus* may colonize most patients, causing minor skin and soft tissue infections in some patients and life-threatening toxic shock syndrome in a very small percentage.[2] Although there are clear microbial factors that regulate these outcomes, we understand so little about how host factors determine highly divergent outcomes in different populations with the same infection. Some associations are well known but poorly understood (eg, sickle cell disease and susceptibility to malaria).[3] In an example of current methods for probing host–pathogen interactions, an article published from the company 23andme described the use of sequencing data and patient-provided infectious disease history to identify novel susceptibility factors.[4] In this Infectious Diseases Specialty Update, we solicited several articles that discuss different aspects of the host side of the host–pathogen relationship.

As researchers seek to define host factors that are important in regulating outcomes with different infections, preclinical animal models offer incredible information. Each model has its limitations, and laboratory animals traditionally are so genetically removed from humans as to restrict the conclusions that could be drawn from these experiments. In this issue, Sarkar and Heise[5] discuss the various animal models for studying infectious diseases with a focus on mouse models. They highlight the promise of the "Collaborative Cross" system, which captures genetic diversity across a population that is much more analogous to humans. They write:

"Because the CC (Collaborative Cross) strains are inbred, they allow investigators to perform the same types of comparative studies across reproducible sets of animals that are conducted with standard inbred strains (ie, C57BL/6). However, because each CC strain possesses a unique combination of genetic material from the original 8 founder strains, CC strains often exhibit unique phenotypes not observed in the original eight founder strains, resulting in the development of new mouse models that better reproduce specific aspects of human disease. Furthermore, by comparing phenotypes between CC strains, investigators can test how host genetic variation affects specific phenotypes, including the response to pathogen challenge, and then map the specific genetic loci responsible for this variation." As the authors indicate, the Collaborative Cross model is now being leveraged across many infectious and noninfectious illnesses to identify new genetic determinants of disease.

In the field of infectious disease diagnostics, the pathogen was the classical target of detection. We use culture-based techniques to grow bacteria, viruses, or fungi in the clinical laboratory, or perhaps use polymerase chain reaction to amplify nucleic acids from the same organisms from sterile body sites.[6] In this issue, Ross et al[7] discuss the incredible advances that have been made in host-based diagnostics. Their group and others have shown that host gene expression analysis has incredible potential in not only discriminating viral versus bacterial infection but also specific viral pathogens. They write: "Transcriptomic approaches present an exciting opportunity for discovery of disease-classifying biomarkers. Although the technology to bring transcriptomic-based tests to the point of care is still being developed, interest and advances by multiple biotechnology companies are paving the way for gene expression-based tests to be available for clinical practice. One simultaneous strength and challenge of transcriptomic approaches is that gene transcription is a dynamic process that evolves over time, in both composition and amplitude, as the corresponding stimulus changes. For example, Woods et al described how the overall intensity

of the transcriptomic response to influenza tracks closely with symptom scores over time, with the observed genomic response significantly preceding changes in clinical scores in symptomatic individuals." It is clear that in the very near future, host-based diagnostics will evolve into an integral part of our clinical algorithms.

Coccidioidomycosis is an endemic fungal infection primarily located in the desert Southwest United States that has been an "emerging" infection for the last 10–20 years.[8,9] Although certain racial and ethnic risk factors for invasive disease are known, more granular data on host factors are lacking. In this issue, Krogstad et al[10] offer a contemporary discussion of what is known about host susceptibility to coccidioidomycosis. They write: "We have described whole-exome sequencing analysis involving a convenience sample of ethnically and racially diverse cohort of 22 adults living in California with extrapulmonary dissemination of coccidioidomycosis. Among these, 16 were men, 8 were African American, 2 were Filipino, and 2 were of Middle Eastern ancestry. In contrast to the analytic approach used by Hsu and Holland, we hypothesized that polymorphisms which predispose to dissemination of *Coccidioides* infection could be *relatively common* alleles among populations with Asian and African ancestry, yet be rare among those of European ancestry, in whom DCM is substantially less common … We identified 3 African-American individuals with alterations in the gene (CHIT1) encoding human chitinase protein are known to reduce or abrogate enzymatic activity … The impact of these genetic variants on chitinase activity and the outcome of coccidioidal infection require verification, but it is conceivable that chitinase release by neutrophils and macrophages interferes with spherule formation and extensive dissemination of Coccidioides."

These studies show how a carefully curated cohort of patients with a specific infectious condition can be used to identify new host susceptibility factors with the latest genetic and sequence-based technologies.

Virus–host interactions have long been studied because an intrinsic part of the interaction is the virus hijacking the host cell machinery for the purpose of replication. In this issue, I contributed a commentary on two well-publicized discoveries of host factors important in hepatitis C and HIV infections.[11] I write: "This commentary focuses on two examples that were highly significant at the time of their discovery, but over time their significance has moved in opposite directions. One has largely been forgotten, whereas the other is still in the news and has evolved into a key component of future strategies for viral cure. Both examples offer lessons about the identification of these factors, the profound influence that a discovery can have on a field over a short-term period, and how quickly things may change with new discoveries." I sincerely hope you find the stories informative and appreciate the perspective each one offers.

I want to end with several thoughts. First, I would like to thank all of the authors for their contributions to this Specialty Update. They are experts in their respective field, and I very much appreciate their time in writing these articles to share their thoughts. Second, I started a new position at the Ann & Robert H. Lurie Children's Hospital of Chicago, and I want to thank my new colleagues for the warm welcome they have offered me. I look forward to what we can accomplish together in the years ahead. Third, this year offered me several reminders of how valuable my family and friends are to me, and how they offer fulfillment and meaning that no professional accomplishment could ever match. I am truly thankful every day for my good fortune, and for what my family and friends contribute to my life. Finally, I want to thank the team at *Clinical Therapeutics*, and we sincerely hope that you enjoy reading this specialty update on "Focusing on the Host Side of Host–Pathogen Interactions."

Ravi Jhaveri, MD
Division of Pediatric Infectious Diseases, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

REFERENCES

1. Sen R, Nayak L, De RK. A review on host-pathogen interactions: classification and prediction. *Eur J Clin Microbiol Infect Dis*. 2016;35:1581–1599.
2. Mulcahy ME, McLoughlin RM. Host-bacterial crosstalk determines Staphylococcus aureus nasal colonization. *Trends Microbiol*. 2016;24:872–886.

3. Williams TN, Mwangi TW, Wambua S, et al. Sickle cell trait and the risk of Plasmodium falciparum malaria and other childhood diseases. *J Infect Dis*. 2005;192:178–186.
4. Tian C, Hromatka BS, Kiefer AK, et al. Genome-wide association and HLA region fine-mapping studies identify susceptibility loci for multiple common infections. *Nat Commun*. 2017;8:599.
5. Sarkar S, Heise M. Mouse models as resources for studying infectious diseases. *Clin Ther*. 2019;41:1912–1922.
6. Miller JM, Binnicker MJ, Campbell S, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the Infectious Diseases Society of America and the American Society for Microbiology. *Clin Infect Dis*. 2018;67:813–816.
7. Ross MH, Zick B, Tsalik EL. Host based diagnostics for acute respiratory infections. *Clin Ther*. 2019;41:1923–1938.
8. McCotter OZ, Benedict K, Engelthaler DM, et al. Update on the epidemiology of coccidioidomycosis in the United States. *Med Mycol*. 2019;57(Suppl 1):S30–S40.
9. Cooksey GS, Nguyen A, Knutson K, et al. Notes from the field: increase in coccidioidomycosis—California, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:833–834.
10. Krogstad P, Johnson R, Garcia-Lloret MI, Heidari A, Butte M. Host-pathogen interactions in coccidioidomycosis prognostic clues and opportunities for novel therapies. *Clin Ther*. 2019;41:1939–1953.
11. Jhaveri R. "Here Today, Gone Tomorrow" or "Here Today, Stay a Long While": the divergent paths of two host factors important in viral infections. *Clin Ther*. 2019;41:1907–1911.