Innate Immunity to Aspergillus Species. Stacy J. Park and Borna Mehrad .......................... 535–551

Summary: All humans are continuously exposed to inhaled Aspergillus conidia, yet healthy hosts clear the organism without developing disease and without the development of antibody- or cell-mediated acquired immunity to this organism. This suggests that for most healthy humans, innate immunity is sufficient to clear the organism. A failure of these defenses results in a uniquely diverse set of illnesses caused by Aspergillus species, which includes diseases caused by the colonization of the respiratory tract, invasive infection, and hypersensitivity. A key concept in immune responses to Aspergillus species is that the susceptibilities of the host determine the morphological form, antigenic structure, and physical location of the fungus. In this review, we summarize the current literature on the multiple layers of innate defenses against Aspergillus species that dictate the outcome of this host-microbe interaction.


Summary: Electron microscopy, considered by some to be an old technique, is still on the forefront of both clinical viral diagnoses and viral ultrastructure and pathogenesis studies. In the diagnostic setting, it is particularly valuable in the surveillance of emerging diseases and potential bioterrorism viruses. In the research arena, modalities such as immuno-electron microscopy, cryo-electron microscopy, and electron tomography have demonstrated how viral structural components fit together, attach to cells, assimilate during replication, and associate with the cellular machinery during replication and egression. These studies provide information for treatment and vaccine strategies.


Summary: Much remains to be learned about the pathogenesis of the different manifestations of dengue virus (DENV) infections in humans. They may range from subclinical infection to dengue fever, dengue hemorrhagic fever (DHF), and eventually dengue shock syndrome (DSS). As both cell tropism and tissue tropism of DENV are considered major determinants in the
There is a critical need for adequate tropism assays, animal models, and human autopsy data. More than 50 years of research on dengue has resulted in a host of literature, which strongly suggests that the pathogenesis of DHF and DSS involves viral virulence factors and detrimental host responses, collectively resulting in abnormal hemostasis and increased vascular permeability. Differential targeting of specific vascular beds is likely to trigger the localized vascular hyperpermeability underlying DSS. A personalized approach to the study of pathogenesis will elucidate the basis of individual risk for development of DHF and DSS as well as identify the genetic and environmental bases for differences in risk for development of severe disease.

Antibacterial-Resistant *Pseudomonas aeruginosa*: Clinical Impact and Complex Regulation of Chromosomally Encoded Resistance Mechanisms. Philip D. Lister, Daniel J. Wolter, and Nancy D. Hanson

Summary: Treatment of infectious diseases becomes more challenging with each passing year. This is especially true for infections caused by the opportunistic pathogen *Pseudomonas aeruginosa*, with its ability to rapidly develop resistance to multiple classes of antibiotics. Although the import of resistance mechanisms on mobile genetic elements is always a concern, the most difficult challenge we face with *P. aeruginosa* is its ability to rapidly develop resistance during the course of treating an infection. The chromosomally encoded AmpC cephalosporinase, the outer membrane porin OprD, and the multidrug efflux pumps are particularly relevant to this therapeutic challenge. The discussion presented in this review highlights the clinical significance of these chromosomally encoded resistance mechanisms, as well as the complex mechanisms/pathways by which *P. aeruginosa* regulates their expression. Although a great deal of knowledge has been gained toward understanding the regulation of AmpC, OprD, and efflux pumps in *P. aeruginosa*, it is clear that we have much to learn about how this resourceful pathogen coregulates different resistance mechanisms to overcome the antibacterial challenges it faces.

Basic Concepts of Microarrays and Potential Applications in Clinical Microbiology. Melissa B. Miller and Yi-Wei Tang

Summary: The introduction of in vitro nucleic acid amplification techniques, led by real-time PCR, into the clinical microbiology laboratory has transformed the laboratory detection of viruses and select bacterial pathogens. However, the progression of the molecular diagnostic revolution currently relies on the ability to efficiently and accurately offer multiplex detection and characterization for a variety of infectious disease pathogens. Microarray analysis has the capability to offer robust multiplex detection but has just started to enter the diagnostic microbiology laboratory. Multiple microarray platforms exist, including printed double-stranded DNA and oligonucleotide arrays, in situ-synthesized arrays, high-density bead arrays, electronic microarrays, and suspension bead arrays. One aim of this paper is to review microarray technology, highlighting technical differences between them and each platform’s advantages and disadvantages. Although the use of microarrays to generate gene expression data has become routine, applications pertinent to clinical microbiology continue to rapidly expand. This review highlights uses of microarray technology that impact diagnostic microbiology, including the detection and identification of pathogens, determination of antimicrobial resistance, epidemiological strain typing, and analysis of microbial infections using host genomic expression and polymorphism profiles.


Summary: Globally, the number of immunosuppressed people increases each year, with the human immunodeficiency virus (HIV) pandemic continuing to spread unabated in many parts of the world. Immunosuppression may also occur in malnourished persons, patients undergoing chemotherapy for malignancy, and those receiving immunosuppressive therapy. Components of
the immune system can be functionally or genetically abnormal as a result of acquired (e.g., caused by HIV infection, lymphoma, or high-dose steroids or other immunosuppressive medications) or congenital illnesses, with more than 120 congenital immunodeficiencies described to date that either affect humoral immunity or compromise T-cell function. All individuals affected by immunosuppression are at risk of infection by opportunistic parasites (such as the microsporidia) as well as those more commonly associated with gastrointestinal disease (such as Giardia). The outcome of infection by enteric protozoan parasites is dependent on absolute CD4⁺ cell counts, with lower counts being associated with more severe disease, more atypical disease, and a greater risk of disseminated disease. This review summarizes our current state of knowledge on the significance of enteric parasitic protozoa as a cause of disease in immuno-suppressed persons and also provides guidance on recent advances in diagnosis and therapy for the control of these important parasites.


Summary: Up to one in four patients infected with human immunodeficiency virus type 1 and given antiretroviral therapy (ART) experiences inflammatory or cellular proliferative disease associated with a preexisting opportunistic infection, which may be subclinical. These immune restoration diseases (IRD) appear to result from the restoration of immunocompetence. IRD associated with intracellular pathogens are characterized by cellular immune responses and/or granulomatous inflammation. Mycobacterial and cryptococcal IRD are attributed to a pathological overproduction of Th1 cytokines. Clinicopathological characteristics of IRD associated with viral infections suggest different pathogenic mechanisms. For example, IRD associated with varicella-zoster virus or JC polyomavirus infection correlate with a CD8 T-cell response in the central nervous system. Exacerbations or de novo presentations of hepatitis associated with hepatitis C virus (HCV) infection following ART may also reflect restoration of pathogen-specific immune responses as titers of HCV-reactive antibodies rise in parallel with liver enzymes and plasma markers of T-cell activation. Correlations between immunological parameters assessed in longitudinal sample sets and clinical presentations are required to illuminate the diverse immunological scenarios described collectively as IRD. Here we present salient clinical features and review progress toward understanding their pathogeneses.

**Plasmid-Mediated Quinolone Resistance: a Multifaceted Threat.** Jacob Strahilevitz, George A. Jacoby, David C. Hooper, and Ari Robicsek. 664–689

Summary: Although plasmid-mediated quinolone resistance (PMQR) was thought not to exist before its discovery in 1998, the past decade has seen an explosion of research characterizing this phenomenon. The best-described form of PMQR is determined by the qnr group of genes. These genes, likely originating in aquatic organisms, code for pentapeptide repeat proteins. These proteins reduce susceptibility to quinolones by protecting the complex of DNA and DNA gyrase or topoisomerase IV enzymes from the inhibitory effect of quinolones. Two additional PMQR mechanisms were recently described. aac(6’)-Ib-cr encodes a variant aminoglycoside acetyltransferase with two amino acid alterations allowing it to inactivate ciprofloxacin through the acetylation of its piperazinyl substituent. oqxAB and qepA encode efflux pumps that extrude quinolones. All of these genes determine relatively small increases in the MICs of quinolones, but these changes are sufficient to facilitate the selection of mutants with higher levels of resistance. The contribution of these genes to the emergence of quinolone resistance is being actively investigated. Several factors suggest their importance in this process, including their increasing ubiquity, their association with other resistance elements, and their emergence simultaneous with the expansion of clinical quinolone resistance. Of concern, these genes are not yet being taken into account in resistance screening by clinical microbiology laboratories.

**Delusional Infestation.** Roland W. Freudenmann and Peter Lepping. 690–732

Summary: This paper aims at familiarizing psychiatric and nonpsychiatric readers with delusional infestation (DI), also known as delusional parasitosis. It is characterized by the fixed belief of being infested with pathogens against all medical evidence. DI is no single disorder but
can occur as a delusional disorder of the somatic type (primary DI) or secondary to numerous other conditions. A set of minimal diagnostic criteria and a classification are provided. Patients with DI pose a truly interdisciplinary problem to the medical system. They avoid psychiatrists and consult dermatologists, microbiologists, or general practitioners but often lose faith in professional medicine. Epidemiology and history suggest that the imaginary pathogens change constantly, while the delusional theme “infestation” is stable and ubiquitous. Patients with self-diagnosed “Morgellons disease” can be seen as a variation of this delusional theme. For clinicians, clinical pathways for efficient diagnostics and etiology-specific treatment are provided. Specialized outpatient clinics in dermatology with a liaison psychiatrist are theoretically best placed to provide care. The most intricate problem is to engage patients in psychiatric therapy. In primary DI, antipsychotics are the treatment of choice, according to limited but sufficient evidence. Pimozide is no longer the treatment of choice for reasons of drug safety. Future research should focus on pathophysiology and the neural basis of DI, as well as on conclusive clinical trials, which are widely lacking. Innovative approaches will be needed, since otherwise patients are unlikely to adhere to any study protocol.