

Clinical Microbiology Reviews

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CONTENTS/SUMMARIES

- Type III Secretion Systems and Disease.** Bryan Coburn, Inna Sekirov,
and B. Brett Finlay 535–549

Summary: Type III secretion systems (T3SSs) are complex bacterial structures that provide gram-negative pathogens with a unique virulence mechanism enabling them to inject bacterial effector proteins directly into the host cell cytoplasm, bypassing the extracellular milieu. Although the effector proteins vary among different T3SS pathogens, common pathogenic mechanisms emerge, including interference with the host cell cytoskeleton to promote attachment and invasion, interference with cellular trafficking processes, cytotoxicity and barrier dysfunction, and immune system subversion. The activity of the T3SSs correlates closely with infection progression and outcome, both in animal models and in human infection. Therefore, to facilitate patient care and improve outcomes, it is important to understand the T3SS-mediated virulence processes and to target T3SSs in therapeutic and prophylactic development efforts.

- Clinical Significance of Human Immunodeficiency Virus Type 1
Replication Fitness.** Carrie Dykes and Lisa M. Demeter 550–578

Summary: The relative fitness of a variant, according to population genetics theory, is that variant's relative contribution to successive generations. Most drug-resistant human immunodeficiency virus type 1 (HIV-1) variants have reduced replication fitness, but at least some of these deficits can be compensated for by the accumulation of second-site mutations. HIV-1 replication fitness also appears to influence the likelihood of a drug-resistant mutant emerging during treatment failure and is postulated to influence clinical outcomes. A variety of assays are available to measure HIV-1 replication fitness in cell culture; however, there is no agreement regarding which assays best correlate with clinical outcomes. A major limitation is that there is no high-throughput assay that incorporates an internal reference strain as a control and utilizes intact virus isolates. Some retrospective studies have demonstrated statistically significant correlations between HIV-1 replication fitness and clinical outcomes in some patient populations. However, different studies disagree as to which clinical outcomes are most closely associated with fitness. This may be in part due to assay design, sample size limitations, and differences in patient populations. In addition, the strength of the correlations between fitness and clinical outcomes is modest, suggesting that, at present, it would be difficult to utilize these assays for clinical management.

Continued on following page

Plasmodium malariae: Parasite and Disease. William E. Collins
and Geoffrey M. Jeffery..... 579–592

Summary: A review of the life history of Plasmodium malariae, the quartan malaria parasite of humans, is presented. Much of the information is based on data obtained from induced infections in humans who were given malaria therapy for the treatment of neurosyphilis between 1940 and 1963. Prepatent periods (i.e., the time until the first day of parasite detection), fever episodes, and maximum parasitemias as a result of infection with P. malariae were obtained and are presented. Experimental and known vectors of the parasite are also discussed. Splenectomized chimpanzees and New World monkeys are readily infected and serve as sources of parasites and antigens for diagnostic and molecular studies. South American monkeys are naturally infected with a parasite known as Plasmodium brasilianum. This parasite appears to be P. malariae that has adapted from humans to grow in monkeys, probably within the last 500 years. Infection with P. malariae is associated with the production of immune complexes in the kidneys and the associated nephrotic syndrome. The essential lesions are a thickening of the glomerular basement membrane and endocapillary cell proliferation. Studies of monkeys infected with P. malariae indicate the same pathology as that demonstrated in humans.

Bacteroides: the Good, the Bad, and the Nitty-Gritty. Hannah M.
Wexler..... 593–621

Summary: Bacteroides species are significant clinical pathogens and are found in most anaerobic infections, with an associated mortality of more than 19%. The bacteria maintain a complex and generally beneficial relationship with the host when retained in the gut, but when they escape this environment they can cause significant pathology, including bacteremia and abscess formation in multiple body sites. Genomic and proteomic analyses have vastly added to our understanding of the manner in which Bacteroides species adapt to, and thrive in, the human gut. A few examples are (i) complex systems to sense and adapt to nutrient availability, (ii) multiple pump systems to expel toxic substances, and (iii) the ability to influence the host immune system so that it controls other (competing) pathogens. B. fragilis, which accounts for only 0.5% of the human colonic flora, is the most commonly isolated anaerobic pathogen due, in part, to its potent virulence factors. Species of the genus Bacteroides have the most antibiotic resistance mechanisms and the highest resistance rates of all anaerobic pathogens. Clinically, Bacteroides species have exhibited increasing resistance to many antibiotics, including ceftioxin, clindamycin, metronidazole, carbapenems, and fluoroquinolones (e.g., gatifloxacin, levofloxacin, and moxifloxacin).

**Human Infection with Fusobacterium necrophorum (Necrobacillosis),
with a Focus on Lemierre's Syndrome.** Terry Riordan 622–659

Summary: Human infection with Fusobacterium necrophorum usually involves F. necrophorum subsp. funduliforme rather than F. necrophorum subsp. necrophorum, which is a common pathogen in animals. Lemierre's syndrome, or postanginal sepsis, is the most common life-threatening manifestation. Tonsillitis is followed by septic thrombophlebitis of the internal jugular vein and then a septicemia with septic emboli in lungs and other sites. Recent evidence suggests that F. necrophorum can be limited to the throat and cause persistent or recurrent tonsillitis. F. necrophorum is unique among non-spore-forming anaerobes, first for its virulence and association with Lemierre's syndrome as a monomicrobial infection and second because it seems probable that it is an exogenously acquired infection. The source of infection is unclear; suggestions include acquisition from animals or human-to-human transmission. Approximately 10% of published cases are associated with infectious mononucleosis, which may facilitate invasion. Recent work suggests that underlying thrombophilia may predispose to internal jugular vein thrombophlebitis. Lemierre's syndrome was relatively common in the preantibiotic era but seemed to virtually disappear with widespread use of antibiotics for upper respiratory tract infection. In the last 15 years there has been a rise in incidence, possibly related to restriction in antibiotic use for sore throat.

Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection. Vincent C. C. Cheng, Susanna K. P. Lau, Patrick C. Y. Woo, and Kwok Yung Yuen . . . 660–694

Summary: Before the emergence of severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) in 2003, only 12 other animal or human coronaviruses were known. The discovery of this virus was soon followed by the discovery of the civet and bat SARS-CoV and the human coronaviruses NL63 and HKU1. Surveillance of coronaviruses in many animal species has increased the number on the list of coronaviruses to at least 36. The explosive nature of the first SARS epidemic, the high mortality, its transient reemergence a year later, and economic disruptions led to a rush on research of the epidemiological, clinical, pathological, immunological, virological, and other basic scientific aspects of the virus and the disease. This research resulted in over 4,000 publications, only some of the most representative works of which could be reviewed in this article. The marked increase in the understanding of the virus and the disease within such a short time has allowed the development of diagnostic tests, animal models, antivirals, vaccines, and epidemiological and infection control measures, which could prove to be useful in randomized control trials if SARS should return. The findings that horseshoe bats are the natural reservoir for SARS-CoV-like virus and that civets are the amplification host highlight the importance of wildlife and biosecurity in farms and wet markets, which can serve as the source and amplification centers for emerging infections.

Fusarium Infections in Immunocompromised Patients. Marcio Nucci and Elias Anaissie . . . 695–704

Summary: Fusarium species cause a broad spectrum of infections in humans, including superficial, locally invasive, and disseminated infections. The clinical form of fusariosis depends largely on the immune status of the host and the portal of entry, with superficial and localized disease occurring mostly in immunocompetent patients and invasive and disseminated disease affecting immunocompromised patients. Risk factors for severe fusariosis include prolonged neutropenia and T-cell immunodeficiency, especially in hematopoietic stem cell transplant recipients with severe graft-versus-host disease. The most frequent presentation of disseminated fusariosis is a combination of characteristic cutaneous lesions and positive blood cultures, with or without lung or sinus involvement. The prognosis is poor and is determined largely by degree of immunosuppression and extent of infection, with virtually a 100% death rate among persistently neutropenic patients with disseminated disease. These infections may be clinically suspected on the basis of a constellation of clinical and laboratory findings, which should lead to prompt therapy. Treatment options include the lipid formulations of amphotericin B, voriconazole, and posaconazole. Prevention of fusarial infection among high-risk patients should be considered.