

# Clinical Microbiology Reviews

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- Emergence of the Severe Syndrome and Mortality Associated with Dengue and Dengue-Like Illness: Historical Records (1890 to 1950) and Their Compatibility with Current Hypotheses on the Shift of Disease Manifestation.** Goro Kuno ..... 186–201

*Summary: Outbreaks of the severe dengue syndrome, dengue hemorrhagic fever (DHF), emerged beginning in the 1950s, marking a dramatic change in the dengue syndrome. While intense investigations in multiple directions have been conducted for many years to elucidate the intrinsic mechanisms conducive to the development of DHF, no consensus has yet emerged. Meanwhile, relatively little attention has been paid to the occurrence of severe dengue and death prior to the 1950s. This comprehensive review was designed to evaluate outbreak records in the early dengue history to better understand the epidemiologic background and other factors that existed before the emergence of DHF outbreaks. By applying a set of stringent criteria to remove unreliable data as much as possible and by interpreting the results conservatively, a short list of etiologically more reliable outbreaks with high mortality was obtained. The results show that severe dengue syndrome, clinically very much compatible with DHF, occurred far more frequently in multiple locations than it had been assumed before; that the magnitudes of mortality in several outbreaks were not negligible; and that the epidemiologic background features shared among these outbreaks in the early period were, with the exceptions of more limited demographic changes, generally similar to the post-1950 conditions.*

- Gastric Helicobacters in Domestic Animals and Nonhuman Primates and Their Significance for Human Health.** Freddy Haesebrouck, Frank Pasmans, Bram Flahou, Koen Chiers, Margo Baele, Tom Meyns, Annemie Decostere, and Richard Ducatelle ..... 202–223

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*Summary: Helicobacters other than Helicobacter pylori have been associated with gastritis, gastric ulcers, and gastric mucosa-associated lymphoid tissue lymphoma in humans. These very fastidious microorganisms with a typical large spiral-shaped morphology were provisionally designated "H. heilmannii," but in fact they comprise at least five different Helicobacter species, all of which are known to colonize the gastric mucosa of animals. H. suis, which has been isolated from the stomachs of pigs, is the most prevalent gastric non-H. pylori Helicobacter species in humans. Other gastric non-H. pylori helicobacters colonizing the human stomach are H. felis, H. salomonis, H. bizzozeronii, and the still-uncultivable "Candidatus Helicobacter heilmannii." These microorganisms are often detected in the stomachs of dogs and cats. "Candidatus Helicobacter bovis" is highly prevalent in the abomasums of cattle but has only occasionally been detected in the stomachs of humans. There are clear indications that gastric non-H. pylori Helicobacter infections in humans originate from animals, and it is likely that transmission to humans occurs through direct contact. Little is known about the virulence factors of these microorganisms. The recent successes with in vitro isolation of non-H. pylori helicobacters from domestic animals open new perspectives for studying these microorganisms and their interactions with the host.*

**Matrix Metalloproteinases as Drug Targets in Infections Caused by Gram-Negative Bacteria and in Septic Shock.** Ineke Vanlaere and Claude Libert .....

224–239

*Summary: The mammalian immune system is optimized to cope effectively with the constant threat of pathogens. However, when the immune system overreacts, sepsis, severe sepsis, or septic shock can develop. Despite extensive research, these conditions remain the leading cause of death in intensive care units. The matrix metalloproteinases (MMPs) constitute a family of proteases that are expressed in developmental, physiological, and pathological processes and also in response to infections. Studies using MMP inhibitors and MMP knockout mice indicate that MMPs play essential roles in infection and in the host defense against infection. This review provides a brief introduction to some basic concepts of infections caused by gram-negative bacteria and reviews reports describing MMP expression and inhibition, as well as studies with MMP-deficient mice in models of infection caused by gram-negative bacteria and of septic shock. We discuss whether MMPs should be considered novel drug targets in infection and septic shock.*

**Pathogen Recognition and Inflammatory Signaling in Innate Immune Defenses.** Trine H. Mogensen .....

240–273

*Summary: The innate immune system constitutes the first line of defense against invading microbial pathogens and relies on a large family of pattern recognition receptors (PRRs), which detect distinct evolutionarily conserved structures on pathogens, termed pathogen-associated molecular patterns (PAMPs). Among the PRRs, the Toll-like receptors have been studied most extensively. Upon PAMP engagement, PRRs trigger intracellular signaling cascades ultimately culminating in the expression of a variety of proinflammatory molecules, which together orchestrate the early host response to infection, and also is a prerequisite for the subsequent activation and shaping of adaptive immunity. In order to avoid immunopathology, this system is tightly regulated by a number of endogenous molecules that limit the magnitude and duration of the inflammatory response. Moreover, pathogenic microbes have developed sophisticated molecular strategies to subvert host defenses by interfering with molecules involved in inflammatory signaling. This review presents current knowledge on pathogen recognition through different families of PRRs and the increasingly complex signaling pathways responsible for activation of an inflammatory and antimicrobial response. Moreover, medical implications are discussed, including the role of PRRs in primary immunodeficiencies and in the pathogenesis of infectious and autoimmune diseases, as well as the possibilities for translation into clinical and therapeutic applications.*

**Infectious Complications Associated with Monoclonal Antibodies and Related Small Molecules.** Edsel Maurice T. Salvana and Robert A. Salata .....

274–290

*Summary: Biologics are increasingly becoming part of routine disease management. As more agents are developed, the challenge of keeping track of indications and side effects is growing. While biologics represent a milestone in targeted and specific therapy, they are not without drawbacks, and the judicious use of these “magic bullets” is essential if their full potential is to be realized. Infectious complications in particular are not an uncommon side effect of therapy, whether as a direct consequence of the agent or because of the underlying disease process. With this in mind, we have reviewed and summarized the risks of infection and the infectious disease-related complications for all FDA-approved monoclonal antibodies and some related small molecules, and we discuss the probable mechanisms involved in immunosuppression as well as recommendations for prophylaxis and treatment of specific disease entities.*

<b>Efflux-Mediated Antifungal Drug Resistance.</b>	Richard D. Cannon, Erwin Lamping, Ann R. Holmes, Kyoko Niimi, Philippe V. Baret, Mikhail V. Keniya, Koichi Tanabe, Masakazu Niimi, Andre Goffeau, and Brian C. Monk .....	291–321
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*Summary: Fungi cause serious infections in the immunocompromised and debilitated, and the incidence of invasive mycoses has increased significantly over the last 3 decades. Slow diagnosis and the relatively few classes of antifungal drugs result in high attributable mortality for systemic fungal infections. Azole antifungals are commonly used for fungal infections, but azole resistance can be a problem for some patient groups. High-level, clinically significant azole resistance usually involves overexpression of plasma membrane efflux pumps belonging to the ATP-binding cassette (ABC) or the major facilitator superfamily class of transporters. The heterologous expression of efflux pumps in model systems, such as *Saccharomyces cerevisiae*, has enabled the functional analysis of efflux pumps from a variety of fungi. Phylogenetic analysis of the ABC pleiotropic drug resistance family has provided a new view of the evolution of this important class of efflux pumps. There are several ways in which the clinical significance of efflux-mediated antifungal drug resistance can be mitigated. Alternative antifungal drugs, such as the echinocandins, that are not efflux pump substrates provide one option. Potential therapeutic approaches that could overcome azole resistance include targeting efflux pump transcriptional regulators and fungal stress response pathways, blockade of energy supply, and direct inhibition of efflux pumps.*

<b>Update on Eosinophilic Meningoencephalitis and Its Clinical Relevance.</b>	Carlos Graeff-Teixeira, Ana Cristina Arámburu da Silva, and Kentaro Yoshimura .....	322–348
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*Summary: Eosinophilic meningoencephalitis is caused by a variety of helminthic infections. These worm-specific infections are named after the causative worm genera, the most common being angiostrongyliasis, gnathostomiasis, toxocariasis, cysticercosis, schistosomiasis, baylisascariasis, and paragonimiasis. Worm parasites enter an organism through ingestion of contaminated water or an intermediate host and can eventually affect the central nervous system (CNS). These infections are potentially serious events leading to sequelae or death, and diagnosis depends on currently limited molecular methods. Identification of parasites in fluids and tissues is rarely possible, while images and clinical examinations do not lead to a definitive diagnosis. Treatment usually requires the concomitant administration of corticoids and anthelmintic drugs, yet new compounds and their extensive and detailed clinical evaluation are much needed. Eosinophilia in fluids may be detected in other infectious and noninfectious conditions, such as neoplastic disease, drug use, and prosthesis reactions. Thus, distinctive identification of eosinophils in fluids is a necessary component in the etiologic diagnosis of CNS infections.*

<b>Enterotoxigenic <i>Bacteroides fragilis</i>: a Rogue among Symbiotes.</b>	Cynthia L. Sears .....	349–369
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*Summary: Enterotoxigenic *Bacteroides fragilis* (ETBF) strains are strains of *B. fragilis* that secrete a 20-kDa heat-labile zinc-dependent metalloprotease toxin termed the *B. fragilis* toxin (BFT). BFT is the only recognized virulence factor specific for ETBF. ETBF strains are*

associated with inflammatory diarrheal disease in children older than 1 year of age and in adults; limited data suggest an association of ETBF colonization with inflammatory bowel disease flare-ups and colorectal cancer. ETBF secretes one of three highly related BFT isoforms. The relationship between BFT isoform and disease expression is unknown. Although the mechanism of action of BFT is incompletely understood, available data suggest that BFT binds to a specific intestinal epithelial cell receptor, stimulating intestinal cell signal transduction pathways that result in cell morphology changes, cleavage of E-cadherin, reduced colonic barrier function, and increased epithelial cell proliferation and cytokine expression (such as the proinflammatory chemokine interleukin-8). Together, the data suggest that in some hosts, ETBF acts via secretion of BFT to induce colitis. However, the full spectrum of clinical disease related to ETBF and the impact of chronic ETBF colonization on the host remain to be defined.

**HLA and Infectious Diseases.** Jenefer M. Blackwell, Sarra E. Jamieson, and David Burgner ..... 370–385

*Summary: Following their discovery in the early 1970s, classical human leukocyte antigen (HLA) loci have been the prototypical candidates for genetic susceptibility to infectious disease. Indeed, the original hypothesis for the extreme variability observed at HLA loci (H-2 in mice) was the major selective pressure from infectious diseases. Now that both the human genome and the molecular basis of innate and acquired immunity are understood in greater detail, do the classical HLA loci still stand out as major genes that determine susceptibility to infectious disease? This review looks afresh at the evidence supporting a role for classical HLA loci in susceptibility to infectious disease, examines the limitations of data reported to date, and discusses current advances in methodology and technology that will potentially lead to greater understanding of their role in infectious diseases in the future.*

***AUTHOR'S CORRECTION***

**Microbiology of Odontogenic Bacteremia: beyond Endocarditis.** N. B. Parahitiyawa, L. J. Jin, W. K. Leung, W. C. Yam, and L. P. Samaranayake ..... 386