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# CLINICAL MICROBIOLOGY REVIEWS



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# Clinical Microbiology Reviews

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## CONTENTS/SUMMARIES



*Summary: The increased use of antibacterial and antifungal agents in recent years has resulted in the development of resistance to these drugs. The significant clinical implication of resistance has led to heightened interest in the study of antimicrobial resistance from different angles. Areas addressed include mechanisms underlying this resistance, improved methods to detect resistance when it occurs, alternate options for the treatment of infections caused by resistant organisms, and strategies to prevent and control the emergence and spread of resistance. In this review, the mode of action of antifungals and their mechanisms of resistance are discussed. Additionally, an attempt is made to discuss the correlation between fungal and bacterial resistance. Antifungals can be grouped into three classes based on their site of action: azoles, which inhibit the synthesis of ergosterol (the main fungal sterol); polyenes, which interact with fungal membrane sterols physicochemically; and 5-fluorocytosine, which inhibits macromolecular synthesis. Many different types of mechanisms contribute to the development of resistance to antifungals. These mechanisms include alteration in drug target, alteration in sterol biosynthesis, reduction in the intercellular concentration of target enzyme, and overexpression of the antifungal drug target. Although the comparison between the mechanisms of resistance to antifungals and antibacterials is necessarily limited by several factors defined in the review, a correlation between the two exists. For example, modification of enzymes which serve as targets for antimicrobial action and the involvement of membrane pumps in the extrusion of drugs are well characterized in both the eukaryotic and prokaryotic cells.*



*Summary: Q fever is a zoonosis with a worldwide distribution with the exception of New Zealand. The disease is caused by Coxiella burnetii, a strictly intracellular, gram-negative bacterium. Many species of mammals, birds, and ticks are reservoirs of C. burnetii in nature. C. burnetii infection is most often latent in animals, with persistent shedding of bacteria into the environment. However, in females intermittent high-level shedding occurs at the time of parturition, with millions of bacteria being released per gram of placenta. Humans are usually infected by contaminated aerosols from domestic animals, particularly after contact with parturient females and their birth products. Although often asymptomatic, Q fever may manifest in humans as an acute disease (mainly as a self-limited febrile illness, pneumonia, or hepatitis)*

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*or as a chronic disease (mainly endocarditis), especially in patients with previous valvulopathy and to a lesser extent in immunocompromised hosts and in pregnant women. Specific diagnosis of Q fever remains based upon serology. Immunoglobulin M (IgM) and IgG antiphase II antibodies are detected 2 to 3 weeks after infection with C. burnetii, whereas the presence of IgG antiphase I C. burnetii antibodies at titers of ≥1:800 by microimmunofluorescence is indicative of chronic Q fever. The tetracyclines are still considered the mainstay of antibiotic therapy of acute Q fever, whereas antibiotic combinations administered over prolonged periods are necessary to prevent relapses in Q fever endocarditis patients. Although the protective role of Q fever vaccination with whole-cell extracts has been established, the population which should be primarily vaccinated remains to be clearly identified. Vaccination should probably be considered in the population at high risk for Q fever endocarditis.*



*Summary: Cryptosporidium parvum is an important cause of diarrhea worldwide. Cryptosporidium causes a potentially life-threatening disease in people with AIDS and contributes significantly to morbidity among children in developing countries. In immunocompetent adults, Cryptosporidium is often associated with waterborne outbreaks of acute diarrheal illness. Recent studies with human volunteers have indicated that Cryptosporidium is highly infectious. Diagnosis of infection with this parasite has relied on identification of acid-fast oocysts in stool; however, new immunoassays or PCR-based assays may increase the sensitivity of detection. Although the mechanism by which Cryptosporidium causes diarrhea is still poorly understood, the parasite and the immune response to it probably combine to impair absorption and enhance secretion within the intestinal tract. Important genetic studies suggest that humans can be infected by at least two genetically distinct types of Cryptosporidium, which may vary in virulence. This may, in part, explain the clinical variability seen in patients with cryptosporidiosis.*



*Summary: The use of and search for drugs and dietary supplements derived from plants have accelerated in recent years. Ethnopharmacologists, botanists, microbiologists, and natural-products chemists are combing the Earth for phytochemicals and "leads" which could be developed for treatment of infectious diseases. While 25 to 50% of current pharmaceuticals are derived from plants, none are used as antimicrobials. Traditional healers have long used plants to prevent or cure infectious conditions; Western medicine is trying to duplicate their successes. Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found in vitro to have antimicrobial properties. This review attempts to summarize the current status of botanical screening efforts, as well as in vivo studies of their effectiveness and toxicity. The structure and antimicrobial properties of phytochemicals are also addressed. Since many of these compounds are currently available as unregulated botanical preparations and their use by the public is increasing rapidly, clinicians need to consider the consequences of patients self-medicating with these preparations.*



*Summary: Recent evolutionary studies reveal that microorganisms including yeasts and fungi are more closely related to mammals than was previously appreciated. Possibly as a consequence, many natural-product toxins that have antimicrobial activity are also toxic to mammalian cells. While this makes it difficult to discover antifungal agents without toxic side effects, it also has enabled detailed studies of drug action in simple genetic model systems. We review here studies on the antifungal actions of antineoplasmic agents. Topics covered include the mechanisms of action of inhibitors of topoisomerases I and II; the immunosuppressants rapamycin, cyclosporin A, and FK506; the phosphatidylinositol 3-kinase inhibitor wortmannin; the angiogenesis inhibitors fumagillin and ovalicin; the HSP90 inhibitor geldanamycin; and agents that inhibit sphingolipid metabolism. In general, these natural products inhibit target proteins conserved from microorganisms to humans. These studies highlight the potential of*

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*microorganisms as screening tools to elucidate the mechanisms of action of novel pharmacological agents with unique effects against specific mammalian cell types, including neoplastic cells. In addition, this analysis suggests that antineoplastic agents and derivatives might find novel indications in the treatment of fungal infections, for which few agents are presently available, toxicity remains a serious concern, and drug resistance is emerging.*



*Summary: The development over the past two decades of molecular methods for manipulation of RNA and DNA has afforded molecular virologists the ability to study viral genomes in detail that has heretofore not been possible. There are many molecular techniques now available for typing and subtyping of viruses. The available methods include restriction fragment length polymorphism analysis, Southern blot analysis, oligonucleotide fingerprint analysis, reverse hybridization, DNA enzyme immunoassay, RNase protection analysis, single-strand conformation polymorphism analysis, heteroduplex mobility assay, nucleotide sequencing, and genome segment length polymorphism analysis. The methods have certain advantages and disadvantages which should be considered in their application to specific viruses or for specific purposes. These techniques are likely to become more widely used in the future for epidemiologic studies and for investigations into the pathophysiology of virus infections.*



*Summary: Infectious coryza is a well-recognized and commonly encountered upper respiratory tract disease of chickens that is caused by the bacterium Haemophilus paragallinarum. The occurrence of recent outbreaks in North America has emphasized that the disease can be significant in meat chickens as well as layer chickens. In developing countries, coryza is commonly complicated by the presence of a range of other infections, resulting in severe disease and significant economic losses. Unusual forms of the disease, involving arthritis and septicemia, again associated with the presence of other pathogens, have been found in South America. Newly recognized bacteria such as Ornithobacterium rhinotracheale and phenotypic variant forms of both H. paragallinarum and close relatives (variant in that they no longer require V-factor for growth in vitro) have increased the difficulty associated with diagnosing the disease. There have been suggestions in both South America and South Africa that new serovars or serovar variants, associated with unusual clinical manifestations and causing vaccine failures, are emerging. Definitive evidence to confirm or deny the role of these "variants" in vaccine failures is currently not available. A new DNA-based diagnostic technique, involving PCR, has been recently described and will greatly assist in the diagnosis of infectious coryza.*



*Summary: Borrelia burgdorferi sensu lato, the spirochete that causes human Lyme borreliosis (LB), is a genetically and phenotypically divergent species. In the past several years, various molecular approaches have been developed and used to determine the phenotypic and genetic heterogeneity within the LB-related spirochetes and their potential association with distinct clinical syndromes. These methods include serotyping, multilocus enzyme electrophoresis, DNA-DNA reassociation analysis, rRNA gene restriction analysis (ribotyping), pulsed-field gel electrophoresis, plasmid fingerprinting, randomly amplified polymorphic DNA fingerprinting analysis, species-specific PCR and PCR-based restriction fragment length polymorphism (RFLP) analysis, and sequence analysis of 16S rRNA and other conserved genes. On the basis of DNA-DNA reassociation analysis, 10 different Borrelia species have been described within the B. burgdorferi sensu lato complex: B. burgdorferi sensu stricto, Borrelia garinii, Borrelia afzelii, Borrelia japonica, Borrelia andersonii, Borrelia valaisiana, Borrelia lusitaniae, Borrelia tanukii, Borrelia turdi, and Borrelia bissettii sp. nov. To date, only B. burgdorferi sensu stricto, B. garinii, and B. afzelii are well known to be responsible for causing human disease. Different*

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