INSTRUCTIONS TO AUTHORS

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REVIEWS

Rifampin Combination Therapy for Nonmycobacterial Infections. Graeme N. Forrest and Kimberly Tamura ......................... 14–34

Summary: The increasing emergence of antimicrobial-resistant organisms, especially methicillin-resistant Staphylococcus aureus (MRSA), has resulted in the increased use of rifampin combination therapy. The data supporting rifampin combination therapy in nonmycobacterial infections are limited by a lack of significantly controlled clinical studies. Therefore, its current use is based upon in vitro or in vivo data or retrospective case series, all with major limitations. A prominent observation from this review is that rifampin combination therapy appears to have improved treatment outcomes in cases in which there is a low organism burden, such as biofilm infections, but is less effective when effective surgery to obtain source control is not performed. The clinical data support rifampin combination therapy for the treatment of prosthetic joint infections due to methicillin-sensitive S. aureus (MSSA) after extensive debridement and for the treatment of prosthetic heart valve infections due to coagulase-negative staphylococci. Importantly, rifampin-vancomycin combination therapy has not shown any benefit over vancomycin monotherapy against MRSA infections either clinically or experimentally. Rifampin combination therapy with daptomycin, fusidic acid, andlinezolid needs further exploration for these severe MRSA infections. Lastly, an assessment of the risk-benefits is needed before the addition of rifampin to other antimicrobials is considered to avoid drug interactions or other drug toxicities.


Summary: Over the past decade, the genus Aeromonas has undergone a number of significant changes of practical importance to clinical microbiologists and scientists alike. In parallel with
the molecular revolution in microbiology, several new species have been identified on a phylogenetic basis, and the genome of the type species A. hydrophila strain ATCC 7966\textsuperscript{T} has been sequenced. In addition to established disease associations, Aeromonas has been shown to be a significant cause of infections associated with natural disasters (hurricanes, tsunamis, and earthquakes) and has been linked to emerging or new illnesses, including near-drowning events, prostatitis, and hemolytic-uremic syndrome. Despite these achievements, issues still remain regarding the role that Aeromonas plays in bacterial gastroenteritis, the extent to which species identification should be attempted in the clinical laboratory, and laboratory reporting of test results from contaminated body sites containing aeromonads. This article provides an extensive review of these topics, in addition to others, such as taxonomic issues, microbial pathogenicity, and antimicrobial resistance markers.

Respiratory Viral Infections in Infants: Causes, Clinical Symptoms, Virology, and Immunology. John S. Tregoning and Jürgen Schwarze ...................................................... 74–98

Summary: In global terms, respiratory viral infection is a major cause of morbidity and mortality. Infancy, in particular, is a time of increased disease susceptibility and severity. Early-life viral infection causes acute illness and can be associated with the development of wheezing and asthma in later life. The most commonly detected viruses are respiratory syncytial virus (RSV), rhinovirus (RV), and influenza virus. In this review we explore the complete picture from epidemiology and virology to clinical impact and immunology. Three striking aspects emerge: The first is the degree of similarity: although the infecting viruses are all different, the clinical outcomes, viral evasion strategies, immune response, and long-term sequelae share many common features. The second is the interplay between the infant immune system and viral infection: the immaturity of the infant immune system alters the outcome of viral infection, but at the same time, viral infection shapes the development of the infant immune system and its future responses. Finally, both the virus and the immune response contribute to damage to the lungs and subsequent disease, and therefore, any prevention or treatment needs to address both of these factors.


Summary: The emergence of vancomycin-intermediate Staphylococcus aureus (VISA) and heterogeneous vancomycin-intermediate Staphylococcus aureus (hVISA) over the past decade has provided a challenge to diagnostic microbiologists to detect these strains, clinicians treating patients with infections due to these strains, and researchers attempting to understand the resistance mechanisms. Recent data show that these strains have been detected globally and in many cases are associated with glycopeptide treatment failure; however, more rigorous clinical studies are required to clearly define the contribution of hVISA to glycopeptide treatment outcomes. It is now becoming clear that sequential point mutations in key global regulatory genes contribute to the hVISA and VISA phenotypes, which are associated predominantly with cell wall thickening and restricted vancomycin access to its site of activity in the division septum; however, the phenotypic features of these strains can vary because the mutations leading to resistance can vary. Interestingly, changes in the staphylococcal surface and expression of agr are likely to impact host-pathogen interactions in hVISA and VISA infections. Given the subtleties of vancomycin susceptibility testing against S. aureus, it is imperative that diagnostic laboratories use well-standardized methods and have a framework for detecting reduced vancomycin susceptibility in S. aureus.

Fungal Sex and Pathogenesis. Geraldine Butler ......................... 140–159

Summary: Human fungal pathogens are associated with diseases ranging from dandruff and skin colonization to invasive bloodstream infections. The major human pathogens belong to the
Candida, Aspergillus, and Cryptococcus clades, and infections have high and increasing morbidity and mortality. Many human fungal pathogens were originally assumed to be asexual. However, recent advances in genome sequencing, which revealed that many species have retained the genes required for the sexual machinery, have dramatically influenced our understanding of the biology of these organisms. Predictions of a rare or cryptic sexual cycle have been supported experimentally for some species. Here, I examine the evidence that human pathogens reproduce sexually. The evolution of the mating-type locus in ascomycetes (including Candida and Aspergillus species) and basidiomycetes (Malassezia and Cryptococcus) is discussed. I provide an overview of how sex is suppressed in different species and discuss the potential associations with pathogenesis.

Three Decades of β-Lactamase Inhibitors. Sarah M. Drawz and Robert A. Bonomo

Summary: Since the introduction of penicillin, β-lactam antibiotics have been the antimicrobial agents of choice. Unfortunately, the efficacy of these life-saving antibiotics is significantly threatened by bacterial β-lactamases. β-Lactamases are now responsible for resistance to penicillins, extended-spectrum cephalosporins, monobactams, and carbapenems. In order to overcome β-lactamase-mediated resistance, β-lactamase inhibitors (clavulanate, sulbactam, and tazobactam) were introduced into clinical practice. These inhibitors greatly enhance the efficacy of their partner β-lactams (amoxicillin, ampicillin, piperacillin, and ticarcillin) in the treatment of serious Enterobacteriaceae and penicillin-resistant staphylococcal infections. However, selective pressure from excess antibiotic use accelerated the emergence of resistance to β-lactam-β-lactamase inhibitor combinations. Furthermore, the prevalence of clinically relevant β-lactamases from other classes that are resistant to inhibition is rapidly increasing. There is an urgent need for effective inhibitors that can restore the activity of β-lactams. Here, we review the catalytic mechanisms of each β-lactamase class. We then discuss approaches for circumventing β-lactamase-mediated resistance, including properties and characteristics of mechanism-based inactivators. We next highlight the mechanisms of action and salient clinical and microbiological features of β-lactamase inhibitors. We also emphasize their therapeutic applications. We close by focusing on novel compounds and the chemical features of these agents that may contribute to a "second generation" of inhibitors. The goal for the next 3 decades will be to design inhibitors that will be effective for more than a single class of β-lactamases.

Impact of Varicella Vaccine on Varicella-Zoster Virus Dynamics. D. Scott Schmid and Aisha O. Jumaan

Summary: The licensure and recommendation of varicella vaccine in the mid-1990s in the United States have led to dramatic declines in varicella incidence and varicella-related deaths and hospitalizations. Varicella outbreaks remain common and occur increasingly in highly vaccinated populations. Breakthrough varicella in vaccinated individuals is characteristically mild, typically with fewer lesions that frequently do not progress to a vesicular stage. As such, the laboratory diagnosis of varicella has grown increasingly important, particularly in outbreak settings. In this review the impact of varicella vaccine on varicella-zoster virus (VZV) disease, arising complications in the effective diagnosis and monitoring of VZV transmission, and the relative strengths and limitations of currently available laboratory diagnostic techniques are all addressed. Since disease symptoms often resolve in outbreak settings before suitable test specimens can be obtained, the need to develop new diagnostic approaches that rely on alternative patient samples is also discussed.

Update on Cyclospora cayetanensis, a Food-Borne and Waterborne Parasite. Ynés R. Ortega and Roxana Sanchez

Summary: The coccidian parasite Cyclospora cayetanensis is recognized as an emerging pathogen that causes protracted diarrhea in humans. The first cases of Cyclospora infection were reported in the late 1970s and were observed among expatriates and travelers in regions where infections are endemic. Since then, Cyclospora has been considered a cause of traveler’s diarrhea. Epidemiological investigations were reported and examined in areas of endemcity

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even before the true identity of Cyclospora was elucidated. Cyclospora was fully characterized in the early 1990s, but it was not until the 1995 Cyclospora outbreak in the United States and Canada that it caught the attention of the public and physicians. The biology, clinical presentation, epidemiology, diagnosis, treatment, and control of cyclosporiasis are reviewed, with a focus on diagnostic assays currently being used for clinical and environmental samples. Challenges and limitations in working with Cyclospora are also discussed.

The Era of Molecular and Other Non-Culture-Based Methods in Diagnosis of Sepsis. Nicasio Mancini, Silvia Carletti, Nadia Ghidoli, Paola Cichero, Roberto Burioni, and Massimo Clementi...

Summary: Sepsis, a leading cause of morbidity and mortality throughout the world, is a clinical syndrome with signs and symptoms relating to an infectious event and the consequent important inflammatory response. From a clinical point of view, sepsis is a continuous process ranging from systemic inflammatory response syndrome (SIRS) to multiple-organ-dysfunction syndrome (MODS). Blood cultures are the current “gold standard” for diagnosis, and they are based on the detection of viable microorganisms present in blood. However, on some occasions, blood cultures have intrinsic limitations in terms of sensitivity and rapidity, and it is not expected that these drawbacks will be overcome by significant improvements in the near future. For these principal reasons, other approaches are therefore needed in association with blood culture to improve the overall diagnostic yield for septic patients. These considerations have represented the rationale for the development of highly sensitive and fast laboratory methods. This review addresses non-culture-based techniques for the diagnosis of sepsis, including molecular and other non-culture-based methods. In particular, the potential clinical role for the sensitive and rapid detection of bacterial and fungal DNA in the development of new diagnostic algorithms is discussed.