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COVER IMAGE



Cover photograph: Echinococcosis, a neglected zoonotic disease, is caused by cestodes (tapeworms) of the genus *Echinococcus* and remains a serious public health concern globally. There are two main species of clinical relevance: *Echinococcus granulosus sensu lato* (causing cystic echinococcosis [CE]) and *Echinococcus multilocularis* (causing alveolar echinococcosis [AE]). The image illustrates some aspects of the life cycle of *E. granulosus* (right side of the image) and *E. multilocularis* (left side of the image) and the pathology and diagnosis of CE and AE. The *Echinococcus* egg is shown as the centerpiece of the illustration, as it is the stage of the life cycle that is released in the feces of a carnivorous definitive host into the external environment and is ingested by and infects a human or herbivorous intermediate host (sheep and other domestic ungulates for CE and rodents and lagomorphs for AE). Eggs hatch in the gut, releasing oncospheres, which pass through the portal and lymphatic vessels, reaching the liver or, less frequently, other organs such as the lungs or brain, where they localize and develop into metacestode larvae. When protoscolexes, produced asexually within the metacestode, are ingested by a definitive host, they develop into mature, egg-producing adult worms. Medical imaging is key to the clinical diagnosis of echinococcosis. On the right side, a CE2 hydatid cyst with daughter cysts as assessed using magnetic resonance imaging is shown, and on the left side, an active alveolar echinococcosis lesion as assessed using positron emission tomography combined with computed tomography is shown. (Concept by Hao Wen, Lucine Vuitton, Tuerhongjiang Tuxun, Jun Li, Dominique A. Vuitton, Wenbao Zhang, and Donald P. McManus; design by Wenbao Zhang; illustration finalized by Madeleine Flynn.) (See related article at e00075-18.) (Copyright © 2019 American Society for Microbiology. All Rights Reserved.)

REVIEWS

Methicillin-Resistant *Staphylococcus aureus* Prosthetic Valve Endocarditis: Pathophysiology, Epidemiology, Clinical Presentation, Diagnosis, and Management

e00041-18

Alicia Galar, Ana A. Weil, David M. Dudzinski, Patricia Muñoz, Mark J. Siedner

Summary: *Staphylococcus aureus* prosthetic valve endocarditis (PVE) remains among the most morbid bacterial infections, with mortality estimates ranging from 40% to 80%. The proportion of PVE cases due to methicillin-resistant *Staphylococcus aureus* (MRSA) has grown in recent decades, to account for more than 15% of cases of *S. aureus* PVE and 6% of all cases of PVE. Because no large studies or clinical trials for PVE have been published, most guidelines on the diagnosis and management of MRSA PVE rely upon expert opinion and data from animal models or related conditions (e.g., coagulase-negative *Staphylococcus* infection). We performed a review of the literature on MRSA PVE to summarize data on pathogenic mechanisms and updates in epidemiology and therapeutic management and to inform diagnostic strategies and priority areas where additional clinical and laboratory data will be particularly useful to guide therapy. Major updates discussed in this review include novel diagnostics, indications for surgical management, the utility of aminoglycosides in medical therapy, and a review of newer antistaphylococcal agents used for the management of MRSA PVE.

The Enterococcus: a Model of Adaptability to Its Environment

e00058-18

Mónica García-Solache, Louis B. Rice

Summary: The genus *Enterococcus* comprises a ubiquitous group of Gram-positive bacteria that are of great relevance to human health for their role as major causative agents of health care-associated infections. The enterococci are resilient and versatile species able to survive under harsh conditions, making them well adapted to the health care environment. Two species cause the majority of enterococcal infections: *Enterococcus faecalis* and *Enterococcus faecium*. Both species demonstrate intrinsic resistance to common antibiotics, such as virtually all cephalosporins, aminoglycosides, clindamycin, and trimethoprim-sulfamethoxazole. Additionally, a remarkably plastic genome allows these two species to readily acquire resistance to further antibiotics, such as high-level aminoglycoside resistance, high-level ampicillin resistance, and

vancomycin resistance, either through mutation or by horizontal transfer of genetic elements conferring resistance determinants.

***Escherichia coli* Pathobionts Associated with Inflammatory Bowel Disease**

e00060-18

Hengameh Chloé Mirsepasi-Lauridsen, Bruce Andrew Vallance, Karen Angeliki Krogfelt, Andreas Munk Petersen

Summary: Gut bacteria play a key role in initiating and maintaining the inflammatory process in the gut tissues of inflammatory bowel disease (IBD) patients, by supplying antigens or other stimulatory factors that trigger immune cell activation. Changes in the composition of the intestinal microbiota in IBD patients compared to that in healthy controls and a reduced diversity of intestinal microbial species are linked to the pathogenesis of IBD. Adherent invasive *Escherichia coli* (AIEC) has been linked to Crohn's disease (CD) patients, while diffusely adherent *E. coli* (DAEC) has been associated with ulcerative colitis (UC). Bacteriological analysis of intestinal biopsy specimens and fecal samples from IBD patients shows an increased number of *E. coli* strains belonging to the B2 phylogenetic group, which are typically known as extraintestinal pathogenic *E. coli* (ExPEC). Results from studies of both cell cultures and animal models reveal pathogenic features of these *E. coli* pathobionts, which may link them to IBD pathogenesis. This suggests that IBD-associated *E. coli* strains play a facilitative role during IBD flares. In this review, we explain IBD-associated *E. coli* and its role in IBD pathogenesis.

Phage Therapy in the Postantibiotic Era

e00066-18

Fernando L. Gordillo Altamirano, Jeremy J. Barr

Summary: Antibiotic resistance is arguably the biggest current threat to global health. An increasing number of infections are becoming harder or almost impossible to treat, carrying high morbidity, mortality, and financial cost. The therapeutic use of bacteriophages, viruses that infect and kill bacteria, is well suited to be part of the multidimensional strategies to combat antibiotic resistance. Although phage therapy was first implemented almost a century ago, it was brought to a standstill after the successful introduction of antibiotics. Now, with the rise of antibiotic resistance, phage therapy is experiencing a well-deserved rebirth. Among the admittedly vast literature recently published on this topic, this review aims to provide a forward-looking perspective on phage therapy and its role in modern society. We cover the key points of the antibiotic resistance crisis and then explain the biological and evolutionary principles that support the use of phages, their interaction with the immune system, and a comparison with antibiotic therapy. By going through up-to-date reports and, whenever possible, human clinical trials, we examine the versatility of phage therapy. We discuss conventional approaches as well as novel strategies, including the use of phage-antibiotic combinations, phage-derived enzymes, exploitation of phage resistance mechanisms, and phage bioengineering. Finally, we discuss the benefits of phage therapy beyond the clinical perspective, including opportunities for scientific outreach and effective education, interdisciplinary collaboration, cultural and economic growth, and even innovative use of social media, making the case that phage therapy is more than just an alternative to antibiotics.

Echinococcosis: Advances in the 21st Century

e00075-18

Hao Wen, Lucine Vuitton, Tuerhongjiang Tuxun, Jun Li, Dominique A. Vuitton, Wenbao Zhang, Donald P. McManus

Summary: Echinococcosis is a zoonosis caused by cestodes of the genus *Echinococcus* (family Taeniidae). This serious and near-cosmopolitan disease continues to be a

significant public health issue, with western China being the area of highest endemicity for both the cystic (CE) and alveolar (AE) forms of echinococcosis. Considerable advances have been made in the 21st century on the genetics, genomics, and molecular epidemiology of the causative parasites, on diagnostic tools, and on treatment techniques and control strategies, including the development and deployment of vaccines. In terms of surgery, new procedures have superseded traditional techniques, and total cystectomy in CE, *ex vivo* resection with autotransplantation in AE, and percutaneous and perendoscopic procedures in both diseases have improved treatment efficacy and the quality of life of patients. In this review, we summarize recent progress on the biology, epidemiology, diagnosis, management, control, and prevention of CE and AE. Currently there is no alternative drug to albendazole to treat echinococcosis, and new compounds are required urgently. Recently acquired genomic and proteomic information can provide a platform for improving diagnosis and for finding new drug and vaccine targets, with direct impact in the future on the control of echinococcosis, which continues to be a global challenge.

Factors That Influence the Immune Response to Vaccination

e00084-18

Petra Zimmermann, Nigel Curtis

Summary: There is substantial variation between individuals in the immune response to vaccination. In this review, we provide an overview of the plethora of studies that have investigated factors that influence humoral and cellular vaccine responses in humans. These include intrinsic host factors (such as age, sex, genetics, and comorbidities), perinatal factors (such as gestational age, birth weight, feeding method, and maternal factors), and extrinsic factors (such as preexisting immunity, microbiota, infections, and antibiotics). Further, environmental factors (such as geographic location, season, family size, and toxins), behavioral factors (such as smoking, alcohol consumption, exercise, and sleep), and nutritional factors (such as body mass index, micronutrients, and enteropathy) also influence how individuals respond to vaccines. Moreover, vaccine factors (such as vaccine type, product, adjuvant, and dose) and administration factors (schedule, site, route, time of vaccination, and coadministered vaccines and other drugs) are also important. An understanding of all these factors and their impacts in the design of vaccine studies and decisions on vaccination schedules offers ways to improve vaccine immunogenicity and efficacy.

Treating Polymicrobial Infections in Chronic Diabetic Wounds

e00091-18

Pranali J. Buch, Yunrong Chai, Edgar D. Goluch

Summary: This review provides a comprehensive summary of issues associated with treating polyclonal bacterial biofilms in chronic diabetic wounds. We use this as a foundation and discuss the alternatives to conventional antibiotics and the emerging need for suitable drug delivery systems. In recent years, extraordinary advances have been made in the field of nanoparticle synthesis and packaging. However, these systems have not been incorporated into the clinic for treatments other than for cancer or severe genetic diseases. We present a unifying perspective on how the field is evolving and the need for an early amalgamation of engineering principles and a biological understanding of underlying phenomena in order to develop a therapy that is translatable to the clinic in a shorter time.

***Candida parapsilosis*: from Genes to the Bedside**

e00111-18

Renáta Tóth, Jozef Nosek, Héctor M. Mora-Montes, Toni Gabaldon, Joseph M. Bliss, Joshua D. Nosanchuk, Siobhán A. Turner, Geraldine Butler, Csaba Vágvölgyi, Attila Gácser

Summary: Patients with suppressed immunity are at the highest risk for hospital-acquired infections. Among these, invasive candidiasis is the most prevalent systemic fungal nosocomial infection. Over recent decades, the combined prevalence of non-*albicans* *Candida* species outranked *Candida albicans* infections in several geographical regions worldwide, highlighting the need to understand their pathobiology in order to develop effective treatment and to prevent future outbreaks. *Candida parapsilosis* is the second or third most frequently isolated *Candida* species from patients. Besides being highly prevalent, its biology differs markedly from that of *C. albicans*, which may be associated with *C. parapsilosis*' increased incidence. Differences in virulence, regulatory and antifungal drug resistance mechanisms, and the patient groups at risk indicate that conclusions drawn from *C. albicans* pathobiology cannot be simply extrapolated to *C. parapsilosis*. Such species-specific characteristics may also influence their recognition and elimination by the host and the efficacy of antifungal drugs. Due to the availability of high-throughput, state-of-the-art experimental tools and molecular genetic methods adapted to *C. parapsilosis*, genome and transcriptome studies are now available that greatly contribute to our understanding of what makes this species a threat. In this review, we summarize 10 years of findings on *C. parapsilosis* pathogenesis, including the species' genetic properties, transcriptome studies, host responses, and molecular mechanisms of virulence. Antifungal susceptibility studies and clinician perspectives are discussed. We also present regional incidence reports in order to provide an updated worldwide epidemiology summary.

NDM Metallo- β -Lactamases and Their Bacterial Producers in Health Care Settings

e00115-18

Wenjing Wu, Yu Feng, Guangmin Tang, Fu Qiao, Alan McNally, Zhiyong Zong

Summary: New Delhi metallo- β -lactamase (NDM) is a metallo- β -lactamase able to hydrolyze almost all β -lactams. Twenty-four NDM variants have been identified in >60 species of 11 bacterial families, and several variants have enhanced carbapenemase activity. *Klebsiella pneumoniae* and *Escherichia coli* are the predominant carriers of *bla*_{NDM}, with certain sequence types (STs) (for *K. pneumoniae*, ST11, ST14, ST15, or ST147; for *E. coli*, ST167, ST410, or ST617) being the most prevalent. NDM-positive strains have been identified worldwide, with the highest prevalence in the Indian subcontinent, the Middle East, and the Balkans. Most *bla*_{NDM}-carrying plasmids belong to limited replicon types (IncX3, IncFII, or IncC). Commonly used phenotypic tests cannot specifically identify NDM. Lateral flow immunoassays specifically detect NDM, and molecular approaches remain the reference methods for detecting *bla*_{NDM}. Polymyxins combined with other agents remain the mainstream options of antimicrobial treatment. Compounds able to inhibit NDM have been found, but none have been approved for clinical use. Outbreaks caused by NDM-positive strains have been reported worldwide, attributable to sources such as contaminated devices. Evidence-based guidelines on prevention and control of carbapenem-resistant Gram-negative bacteria are available, although none are specific for NDM-positive strains. NDM will remain a severe challenge in health care settings, and more studies on appropriate countermeasures are required.