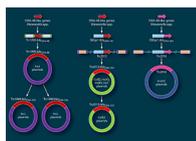




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COVER IMAGE



Cover photograph: The origin and evolution of OXA-48-like carbapenemases. The nucleotide similarities and genetic structures flanking the OXA-48-like carbapenemase genes suggest that *bla*_{OXA-48}, *bla*_{OXA-181}, and *bla*_{OXA-204} were derived from different *Shewanella xiamenensis* isolates through distinct transposition processes. OXA-162 and OXA-244 are derivatives of OXA-48 (left panel), while OXA-232 is a derivative of OXA-181 (middle panel). (See related article at e00102-19.) (Copyright © 2019 American Society for Microbiology. All Rights Reserved.)

ACKNOWLEDGMENT OF REVIEWERS

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e00174-19

Jo-Anne H. Young

PRACTICAL GUIDANCE FOR CLINICAL MICROBIOLOGY

A Comprehensive Update on the Problem of Blood Culture Contamination and a Discussion of Methods for Addressing the Problem

e00009-19

Gary V. Doern, Karen C. Carroll, Daniel J. Diekema, Kevin W. Garey, Mark E. Rupp, Melvin P. Weinstein, Daniel J. Sexton

Summary: In this review, we present a comprehensive discussion of matters related to the problem of blood culture contamination. Issues addressed include the scope and magnitude of the problem, the bacteria most often recognized as contaminants, the impact of blood culture contamination on clinical microbiology laboratory function, the economic and clinical ramifications of contamination, and, perhaps most importantly, a systematic discussion of solutions to the problem. We conclude by providing a series of unanswered questions that pertain to this important issue.

REVIEWS

Chagas Disease in the United States: a Public Health Approach

e00023-19

Caryn Bern, Louisa A. Messenger, Jeffrey D. Whitman, James H. Maguire

Summary: *Trypanosoma cruzi* is the etiological agent of Chagas disease, usually transmitted by triatomine vectors. An estimated 20 to 30% of infected individuals develop potentially lethal cardiac or gastrointestinal disease. Sylvatic transmission cycles exist in the southern United States, involving 11 triatomine vector species and infected mammals such as rodents, opossums, and dogs. Nevertheless, imported chronic *T. cruzi* infections in migrants from Latin America vastly outnumber locally acquired human cases. Benznidazole is now FDA approved, and clinical and public health efforts are under way by researchers and health departments in a number of states. Making progress will require efforts to improve awareness among providers and patients, data on diagnostic test performance and expanded availability of confirmatory testing, and evidence-based strategies to improve access to appropriate management of Chagas disease in the United States.

Laboratory Diagnosis of Human Brucellosis

e00073-19

Pablo Yagupsky, Pilar Morata, Juan D. Colmenero

Summary: The clinical presentation of brucellosis in humans is variable and unspecific, and thus, laboratory corroboration of the diagnosis is essential for the patient's proper treatment. The diagnosis of brucellar infections can be made by culture, serological tests, and nucleic acid amplification assays. Modern automated blood culture systems

enable detection of acute cases of brucellosis within the routine 5- to 7-day incubation protocol employed in clinical microbiology laboratories, although a longer incubation and performance of blind subcultures may be needed for protracted cases. Serological tests, though they lack specificity and provide results that may be difficult to interpret in individuals repeatedly exposed to *Brucella* organisms, nevertheless remain a diagnostic cornerstone in resource-poor countries. Nucleic acid amplification assays combine exquisite sensitivity, specificity, and safety and enable rapid diagnosis of the disease. However, long-term persistence of positive molecular test results in patients that have apparently fully recovered is common and has unclear clinical significance and therapeutic implications. Therefore, as long as there are no sufficiently validated commercial tests or studies that demonstrate an adequate interlaboratory reproducibility of the different homemade PCR assays, cultures and serological methods will remain the primary tools for the diagnosis and posttherapeutic follow-up of human brucellosis.

Tuberculosis Vaccine Development: Progress in Clinical Evaluation

e00100-19

Suraj B. Sable, James E. Posey, Thomas J. Scriba

Summary: Tuberculosis (TB) is the leading killer among all infectious diseases worldwide despite extensive use of the *Mycobacterium bovis* bacille Calmette-Guérin (BCG) vaccine. A safer and more effective vaccine than BCG is urgently required. More than a dozen TB vaccine candidates are under active evaluation in clinical trials aimed to prevent infection, disease, and recurrence. After decades of extensive research, renewed promise of an effective vaccine against this ancient airborne disease has recently emerged. In two innovative phase 2b vaccine clinical trials, one for the prevention of *Mycobacterium tuberculosis* infection in healthy adolescents and another for the prevention of TB disease in *M. tuberculosis*-infected adults, efficacy signals were observed. These breakthroughs, based on the greatly expanded knowledge of the *M. tuberculosis* infection spectrum, immunology of TB, and vaccine platforms, have reinvigorated the TB vaccine field. Here, we review our current understanding of natural immunity to TB, limitations in BCG immunity that are guiding vaccinologists to design novel TB vaccine candidates and concepts, and the desired attributes of a modern TB vaccine. We provide an overview of the progress of TB vaccine candidates in clinical evaluation, perspectives on the challenges faced by current vaccine concepts, and potential avenues to build on recent successes and accelerate the TB vaccine research-and-development trajectory.

Rapid Growth and Metabolism of Uropathogenic *Escherichia coli* in Relation to Urine Composition

e00101-19

Larry Reitzer, Philippe Zimmern

Summary: Uropathogenic *Escherichia coli* (UPEC) strains cause a majority of urinary tract infections (UTIs). Since UPEC strains can become antibiotic resistant, adjunct or alternate therapies are urgently needed. UPEC strains grow extremely rapidly in patients with UTIs. Thus, this review focuses on the relation between urine composition and UPEC growth and metabolism. Compilation of urinary components from two major data sources suggests the presence of sufficient amino acids and carbohydrates as energy sources and abundant phosphorus, sulfur, and nitrogen sources. In a mouse UTI model, mutants lacking enzymes of the tricarboxylic acid cycle, gluconeogenesis, and the nonoxidative branch of the pentose cycle are less competitive than the corresponding parental strains, which is consistent with amino acids as major energy sources. Other evidence suggests that carbohydrates are required energy sources. UPEC strains in urine *ex vivo* and *in vivo* express transporters for peptides, amino acids, carbohydrates, and iron and genes associated with nitrogen limitation, amino acid synthesis, nucleotide synthesis, and nucleotide salvage. Mouse models confirm the

requirement for many, but not all, of these genes. Laboratory evolution studies suggest that rapid nutrient uptake without metabolic rewiring is sufficient to account for rapid growth. Proteins and pathways required for rapid growth should be considered potential targets for alternate or adjunct therapies.

The Global Ascendancy of OXA-48-Type Carbapenemases

e00102-19

Johann D. D. Pitout, Gisele Peirano, Marleen M. Kock, Kathy-Anne Strydom, Yasufumi Matsumura

Summary: Surveillance studies have shown that OXA-48-like carbapenemases are the most common carbapenemases in *Enterobacteriales* in certain regions of the world and are being introduced on a regular basis into regions of nonendemicity, where they are responsible for nosocomial outbreaks. OXA-48, OXA-181, OXA-232, OXA-204, OXA-162, and OXA-244, in that order, are the most common enzymes identified among the OXA-48-like carbapenemase group. OXA-48 is associated with different Tn1999 variants on IncI plasmids and is endemic in North Africa and the Middle East. OXA-162 and OXA-244 are derivatives of OXA-48 and are present in Europe. OXA-181 and OXA-232 are associated with ISEcp1, Tn2013 on ColE2, and IncX3 types of plasmids and are endemic in the Indian subcontinent (e.g., India, Bangladesh, Pakistan, and Sri Lanka) and certain sub-Saharan African countries. Overall, clonal dissemination plays a minor role in the spread of OXA-48-like carbapenemases, but certain high-risk clones (e.g., *Klebsiella pneumoniae* sequence type 147 [ST147], ST307, ST15, and ST14 and *Escherichia coli* ST38 and ST410) have been associated with the global dispersion of OXA-48, OXA-181, OXA-232, and OXA-204. Chromosomal integration of *bla*_{OXA-48} within Tn6237 occurred among *E. coli* ST38 isolates, especially in the United Kingdom. The detection of *Enterobacteriales* with OXA-48-like enzymes using phenotypic methods has improved recently but remains challenging for clinical laboratories in regions of nonendemicity. Identification of the specific type of OXA-48-like enzyme requires sequencing of the corresponding genes. Bacteria (especially *K. pneumoniae* and *E. coli*) with *bla*_{OXA-48}, *bla*_{OXA-181}, and *bla*_{OXA-232} are emerging in different parts of the world and are most likely underreported due to problems with the laboratory detection of these enzymes. The medical community should be aware of the looming threat that is posed by bacteria with OXA-48-like carbapenemases.

The Role of the BCL-2 Family of Proteins in HIV-1 Pathogenesis and Persistence

e00107-19

Aswath P. Chandrasekar, Nathan W. Cummins, Andrew D. Badley

Summary: Advances in HIV-1 therapy have transformed the once fatal infection into a manageable, chronic condition, yet the search for a widely applicable approach to cure remains elusive. The ineffectiveness of antiretroviral therapy (ART) in reducing the size of the HIV-1 latent reservoir has prompted investigation into the mechanisms of HIV-1 latency and immune escape. One of the major regulators of apoptosis, the BCL-2 protein, alongside its homologous family members, is a major target of HIV-1-induced change. Recent studies have now demonstrated the association of this protein with cells that support proviral forms in the setting of latency and have helped identify BCL-2 as a novel and promising therapeutic target for HIV-1 therapy directed at possible cure. This review aims to systematically review the interactions of HIV-1 with BCL-2 and its homologs and to examine the possibility of using BCL-2 inhibitors in the study and elimination of the latent reservoir.

Early Events in Coccidioidomycosis

e00112-19

Fariba M. Donovan, Lisa Shubitz, Daniel Powell, Marc Orbach, Jeffrey Frelinger, John N. Galgiani

Summary: Since its description nearly 130 years ago, hundreds of studies have deepened our understanding of coccidioidomycosis, also known as valley fever (VF), and provided useful diagnostic tests and treatments for the disease caused by the

dimorphic fungi *Coccidioides* spp. In general, most of the literature has addressed well-established infections and has described patients who have experienced major complications. In contrast, little attention has been given to the earliest consequences of the pathogen-host interaction and its implications for disease manifestation, progression, and resolution. The purpose of this review is to highlight published studies on early coccidioidomycosis, identify gaps in our knowledge, and suggest new or former research areas that might be or remain fertile ground for insight into the early stages of this invasive fungal disease.

Performance of Zika Assays in the Context of *Toxoplasma gondii*, Parvovirus B19, Rubella Virus, and Cytomegalovirus (TORCH) Diagnostic Assays e00130-18

Bettie Voordouw, Barry Rockx, Thomas Jaenisch, Pieter Fraaij, Philippe Mayaud, Ann Vossen, Marion Koopmans

Summary: Infections during pregnancy that may cause congenital abnormalities have been recognized for decades, but their diagnosis is challenging. This was again illustrated with the emergence of Zika virus (ZIKV), highlighting the inherent difficulties in estimating the extent of pre- and postnatal ZIKV complications because of the difficulties in establishing definitive diagnoses. We reviewed the epidemiology, infection kinetics, and diagnostic methods used for *Toxoplasma gondii*, parvovirus B19, rubella virus, and cytomegalovirus (TORCH) infections and compared the results with current knowledge of ZIKV diagnostic assays to provide a basis for the inclusion of ZIKV in the TORCH complex evaluations. Similarities between TORCH pathogens and ZIKV support inclusion of ZIKV as an emerging TORCH infection. Our review evaluates the diagnostic performance of various TORCH diagnostic assays for maternal screening, fetal screening, and neonatal screening. We show that the sensitivity, specificity, and positive and negative predictive value of TORCH complex pathogens are widely variable, stressing the importance of confirmatory testing and the need for novel techniques for earlier and accurate diagnosis of maternal and congenital infections. In this context it is also important to acknowledge different needs and access to care for different geographic and resource settings.

***Aspergillus fumigatus* and Aspergillosis in 2019** e00140-18

Jean-Paul Latgé, Georgios Chamilos

Summary: *Aspergillus fumigatus* is a saprotrophic fungus; its primary habitat is the soil. In its ecological niche, the fungus has learned how to adapt and proliferate in hostile environments. This capacity has helped the fungus to resist and survive against human host defenses and, further, to be responsible for one of the most devastating lung infections in terms of morbidity and mortality. In this review, we will provide (i) a description of the biological cycle of *A. fumigatus*; (ii) a historical perspective of the spectrum of aspergillus disease and the current epidemiological status of these infections; (iii) an analysis of the modes of immune response against *Aspergillus* in immunocompetent and immunocompromised patients; (iv) an understanding of the pathways responsible for fungal virulence and their host molecular targets, with a specific focus on the cell wall; (v) the current status of the diagnosis of different clinical syndromes; and (vi) an overview of the available antifungal armamentarium and the therapeutic strategies in the clinical context. In addition, the emergence of new concepts, such as nutritional immunity and the integration and rewiring of multiple fungal metabolic activities occurring during lung invasion, has helped us to redefine the opportunistic pathogenesis of *A. fumigatus*.