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Preface: Our Pathogens Are Not Standing Still and Neither Can We xiii

James E. Kirby

Rapid Susceptibility Testing Methods 333

Kenneth P. Smith and James E. Kirby

With emerging antimicrobial resistance, rapid antimicrobial susceptibility testing (AST) is needed to provide early definitive therapeutic guidance to optimize patient outcome. Genotypic methods are fast, but can identify only a subset of known resistance elements. Phenotypic methods determine clinically predictive minimal inhibitory concentrations and include very sensitive optical and biophysical methods to detect changes in replication or physiology of pathogens in response to antibiotics. For the potential of rapid AST to be fully realized, results must be linked with robust decision support solutions that will implement therapeutic changes in real time.

When One Drug Is Not Enough: Context, Methodology, and Future Prospects in Antibacterial Synergy Testing 345

Thea Brennan-Krohn and James E. Kirby

Antibacterial combinations have long been used to accomplish a variety of therapeutic goals, including prevention of resistance and enhanced antimicrobial activity. In vitro synergy testing methods, including the checkerboard array, the time-kill study, diffusion assays, and pharmacokinetic/pharmacodynamic models, are used commonly in the research setting, but are not routinely performed in the clinical microbiology laboratory because of test complexity and uncertainty about their predictive value for patient outcomes. Optimized synergy testing techniques and better data on the relationship between in vitro results and clinical outcomes are needed to guide the rational use of antimicrobial combinations in the multidrug resistance era.

Clinical Microbiology in Underresourced Settings 359

Ellen Jo Baron

The article discusses the environment of laboratory diagnostic bacteriology testing in several underresourced settings experienced by the author. The major global infectious diseases are usually managed with government or donor-supported systems, whereas basic laboratory testing for bacterial infections has no formal global programs. The causes of many of those diseases can be detected using simple manual bacteriologic methods available in most resource-limited environments; however, the challenges of building laboratory capacity in those settings are many. Positive and negative aspects of developing such capacities in selected locations are presented.

Total Laboratory Automation: What Is Gained, What Is Lost, and Who Can Afford It? 371

Richard B. Thomson Jr and Erin McElvania

The first clinical microbiology laboratory in the United States adopted total automation for bacteriology processing in 2014. Since then, others have followed with installation of either the BD Kiestra TLA or the Copan WAS-PLab. This article discusses commercially available automated systems in the United States; why automation is needed; and quality improvements, efficiency, and cost savings associated with automation. After learning how these systems are used, gains and losses experienced, and how one can afford the most expensive equipment ever purchased for clinical microbiology laboratories, the question is, how can one afford not to purchase one of these microbiology automation systems?

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight: The Revolution in Progress 391

Alexandra L. Bryson, Emily M. Hill, and Christopher D. Doern

This article summarizes recent advances in the application of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) to new areas of infectious diseases diagnostics. We discuss progress toward routine identification of mycobacteria and filamentous fungi and direct identification of pathogens from clinical specimens. Of greatest interest is the use of MALDI-TOF MS for identifying organisms from positive blood cultures and from clinical specimens such as urine. Last, We highlight some exciting new possibilities for MALDI-TOF MS phenotypic susceptibility testing for bacteria and yeast.

Next-Generation Sequencing in Clinical Microbiology: Are We There Yet? 405

Stephanie L. Mitchell and Patricia J. Simner

Next-generation sequencing (NGS) applications have been transitioning from research tools to diagnostic methods and are becoming more commonplace in clinical microbiology laboratories. These applications include (1) whole-genome sequencing, (2) targeted next-generation sequencing methods, and (3) metagenomic next-generation sequencing. The introduction of these methods into the clinical microbiology laboratory has led to the theoretic question of "Will NGS-based methods supplant traditional methods for strain typing, identification, and antimicrobial susceptibility prediction?" The authors address this question and discuss where we are at now with clinical NGS applications for infectious diseases, what does the future hold, and at what cost?

Distributed Microbiology Testing: Bringing Infectious Disease Diagnostics to Point of Care 419

David R. Peaper, Thomas Durant, and Sheldon Campbell

We discuss the current practice of point-of-care diagnostics in infectious diseases as methods transition from antigen-based to molecular, and beyond simple molecular to the next generations of point-of-care testing methods. We evaluate the role of point-of-care at different sites of care and describe and evaluate trends likely to be driven by advances in

molecular methodology, emerging biomarkers, and informatics. We describe strengths, weaknesses, opportunities, and threats to the development of point-of-care diagnostics in the near (1–10 years) and more distant (10–20 years) future.

Direct-from-Specimen Pathogen Identification: Evolution of Syndromic Panels 433

Marc Roger Couturier and Jennifer Dien Bard

This article describes the current state of the art with regards to commercially available syndromic panels for blood stream infections, gastrointestinal pathogen detection, respiratory tract infections, and central nervous system infections, while providing a provocative and speculative look into the future of syndromic panel testing for infectious diseases.

Predicting Bacterial Versus Viral Infection, or None of the Above: Current and Future Prospects of Biomarkers 453

Stefan Riedel

Sepsis and pneumonia cause significant morbidity and mortality worldwide. Despite improvements in diagnostic methodologies for organism identification, the early recognition and further risk stratification of these infections can be challenging. Although traditional clinical scoring systems are beneficial for the management of sepsis and pneumonia, biomarkers supporting the diagnosis and management of these infectious diseases are needed. Many biomarkers have been identified and there is no lack of studies and meta-analyses assessing the utility of biomarkers. Focusing primarily on sepsis and pneumonia, this article discusses the most commonly used biomarkers for which clinical laboratory testing methods are available.

What the Clinical Microbiologist Should Know About Pharmacokinetics/ Pharmacodynamics in the Era of Emerging Multidrug Resistance: Focusing on β -Lactam/ β -Lactamase Inhibitor Combinations 473

Henrietta Abodakpi, Audrey Wanger, and Vincent H. Tam

As a class, β -lactamase inhibitors have proved successful in extending the clinical utility of β -lactam antibiotics by circumventing β -lactamase-mediated resistance. However, the rapid evolution of these β -lactamases calls for a critical reevaluation of the relationships between susceptibility, drug exposures, and bacterial response. The existing paradigm for in vitro susceptibility testing and development of β -lactam/ β -lactamase inhibitor combinations may not optimally facilitate clinical use. Thus, alternative approaches for pairing these combinations and evaluating in vitro susceptibility are needed to provide better guidance to clinicians.

Mapping the Road to the Future: Training the Next Generation of Clinical Microbiologists, from Technologist to Laboratory Director 487

Peter H. Gilligan and Martha H. McGee

Rapidly changing technology in the clinical microbiology laboratory requires a highly skilled workforce. The current clinical microbiology

workforce is aging with a wave of retirements currently unfolding. Key competencies that will be needed for the next generation of microbiologists include strong analytical skills, adaptability, and the willingness to be life-long learners. Experiential learning is a key component of the initial learning environment for medical laboratory scientists and technicians. Continuing education in clinical microbiology must reflect the changes in technology whereby learners are more comfortable in an electronic learning environment, such as TED Talks and YouTube.

We Cannot Do It Alone: The Intersection of Public Health, Public Policy, and Clinical Microbiology **499**

Rose A. Lee and James E. Kirby

Infectious diseases by definition spread and therefore have impact beyond local hospitals and institutions where they occur. With increasingly complex and worrisome infectious disease evolution including emergence of multidrug resistance, regional, national, and international agencies and resources must work hand in hand with local clinical microbiology laboratories to address these global threats. Described are examples of such resources, both existing and aspirational, that will be needed to address the infectious disease challenges ahead. The authors comment on several instances of entrenched policy that are nonproductive and may be worthy of revision to address unmet needs in infectious disease diagnostics.

Pictorial Illustration

What Is the Future of Clinical Microbiology? **509**

Alexander J. McAdam

Clinical microbiology has advanced tremendously in the past 10 years. In this comic, the role of technology, the need for skilled microbiologists, and the meaning of progress in clinical microbiology are considered.