Diagnostic Microbiology of the Immunocompromised Host
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The subject matter of this book is focused on the implementation of diagnostic techniques for a special purpose, that of accurately and rapidly diagnosing infections of the immunocompromised host. In addition to the usual litany of pathogens that threaten all of us, patients with a compromised immune status are susceptible to normally harmless microbial cohabitants. Such infections may become invasive and life-threatening, in recent years affecting growing numbers of patients. This book provides a timely, up-to-date, and comprehensive summary of the ever-expanding array of technologies used to diagnose these infections and to monitor the effectiveness of specific therapies. For immunocompromised patients, the timing could not be better.

Many innovations in diagnostics over the past few decades have been fueled by the needs of specific patient populations. Immunocompromised patients are especially vulnerable to diagnostic delays because the time to intervention can have a dramatic impact on therapeutic efficacy. Only a few years ago, blood culture bottles were tested in “first morning batches” by Gram stain and culture, necessitating long delays in some cases. Differential counts were tallied by hand. In many pathology departments in the 1960s, immunoassays were performed in batches, perhaps once per week, within specialized laboratories built for containment of the radioisotopes used to label antibodies. Rabbit antisera, sometimes collected from local farm animals, was radioiodinated with Bolton-Hunter reagent to generate the key diagnostic ingredient.

Fortunately, in clinical laboratories, as elsewhere in medicine, times have changed. Nonisotopic immunoassays were developed that could be automated, and more recently, random access immunoassay systems have been developed to eliminate batching requirements and improve turnaround time. Stat immunoassays for a variety of indications are now a reality, if not the standard of practice. Blood culture systems have been developed to allow continuous monitoring for the presence of microbial growth; these systems have largely replaced batch systems that require blind subculture. The fundamental impact of this technology is that it allows for delivery of “real-time” results. For immunocompromised patients, this need for speed is especially critical because infections in these patients often evolve quickly into life-threatening events. Earlier diagnoses can translate into earlier specific therapeutic interventions, which are more likely to result in favorable patient outcomes.

Nucleic acid amplification techniques occupy an increasingly important role in diagnosis and monitoring of infection in immunocompromised patients, and many chapters of this book are appropriately focused on detection of nucleic acid targets. Though the pathogens themselves come from entirely different phylogenetic domains, they are all similar in that they harbor genetic signatures in their genomes that can be used to identify them, quantify infectious burdens, determine virulence, and assess susceptibility or resistance to available drugs. Clumsy, contamination-prone techniques have largely been replaced with real-time detection technology performed in closed systems, and DNA sequencing and microarray technologies developed under the auspices of the human genome project are making steady inroads into clinical practice. Diagnosticians have taken great leaps forward in their level of overall sophistication and familiarity with this technology. Phylogenetic analysis and identification of bacteria, fungi, and viruses by direct DNA sequencing are quickly entering the mainstream and will require us to add a few new words, such as “bootstrapping” and “parsimonious,” to our vocabulary. Microarray technology has yet to enter into routine diagnostic use for infectious disease applica-
tions, but it is only a matter of time until that happens.

As promising and important as it is, however, the practice of molecular diagnostics is currently more akin to that of the radioimmunoassay laboratory of the 1960s. Despite the speed of the underlying detection technologies, the requirements of specimen processing impose practical limits on turnaround time. As molecular methods evolve, the technology needs to keep up with requirements for optimal clinical management. For example, febrile patients who are immunocompromised would benefit greatly from rapid, on-demand testing of bacterial and fungal causes of sepsis, without the need to wait for initial blood culture results. Proof of concept of this approach has now been provided by at least one system, which is designed to detect and differentiate 23 pathogens by using broad-range PCR. As technologies like this become available, and as they evolve from batch mode to on-demand formats, they will have an ever greater impact on patient treatment and management. As real-time molecular diagnostic technology improves, so should the delivery of real-time patient results.

Few challenges are as urgent as determining definitively the cause of fever in an immunocompromised patient, given the sheer range of diagnostic possibilities. Fortunately, practitioners have filled this apparent diagnostic void with user-developed assays, and diagnostic companies themselves appear to be rising to the task. Hopefully, this trend will continue. Meeting the diagnostic challenges of immunocompromised patients will ultimately have broader implications; as described in this book, there is the potential to improve access to this technology for all patients, where and when they need it most.

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Over the past quarter century, health care of immunocompromised patients has grown progressively in importance. These individuals require high-intensity services and specialized care, often for a prolonged period of time. They are susceptible to a wide range of infectious diseases, which may manifest quite differently from those in an immunocompetent host. There are marked differences in how health care is delivered to such high-risk patients. Proper care depends on the etiology and degree of immune suppression as well as on underlying patient characteristics, such as demographics, nutritional status, and ongoing disease processes. Differences in clinical care include aspects of infection control practices, infectious disease prophylaxis, immune modulation, and pharmacologic therapy. In addition, the use and interpretation of laboratory tests, particularly tests for microorganisms, must be tailored carefully to fit these patients. Evidence-based diagnostic algorithms for the immunocompromised are evolving; however, many clinicians and laboratory professionals are challenged to best utilize the growing array of diagnostic tools at their disposal. Certainly there are books containing information on clinical testing; however, no standard laboratory reference focuses heavily on issues unique to the immunocompromised population. It is the goal of the authors to consolidate such discussions in a single, easily referenced text that can be used by clinical health care providers and laboratory professionals alike.

This book provides several approaches to the topic. The stage is set in the first section, wherein the essence of the problem is defined. That is, what are the causes of immune suppression, who are the populations at risk for infections, and to which infections are they prone? In Section II, the application of laboratory diagnostic methods is discussed, primarily in an organism-by-organism fashion, while in Section III, discussions are based on the organ system involved. Readers will find that these two approaches are complementary.

While in many cases the clinician may be more comfortable with an organ system approach, a focus on individual pathogens may be more useful in deciding upon screening strategies or follow-up of a known infection. Although laboratory professionals may turn most frequently to chapters on individual infectious agents, the systemic perspective will bring added value in making decisions on which new diagnostic methods to introduce in the laboratory. These sections will also be useful for a review of specimen-specific culture workup and exceptions to the rules, which may apply to immunocompromised patient units or clinics. In addition, many chapters include flow charts suggesting diagnostic pathways. We hope that these sections will provide a way to help to synthesize the material presented in the text into practical, user-friendly algorithms that can be applied to everyday patient care challenges. The concluding segment of the book pushes the envelope of current diagnostics, with a look at future trends in the diagnosis of infectious diseases in the immunocompromised patient. We hope that this section will enable health care facilities that treat these patients to plan for the future and to assess new technology from a global cost-benefit perspective as they attempt to wisely use scarce resources in the future.

This book is intended to have broad appeal to laboratory professionals, infectious disease physicians, oncologists, and other health care providers who play important roles in the health care of immunocompromised patients. The editorial board, as well as the contributors, comprise a diverse group of both clinical infectious disease practitioners and laboratory-based diagnosticians. We hope that this book will fill a void in many health care providers’ libraries and contribute positively to the care of...
these increasingly complex patients. By sharing this information and working effectively together with a patient-focused approach, it is our hope that we can help to face the challenges of providing optimal diagnostic services to the immunocompromised patients in our care.

We extend our heartfelt thanks to all of the chapter authors, who devoted so much of their time and expertise to this project. Working with such a fine group of professionals has been our pleasure. We are also grateful for the support and patience of our families while we immersed ourselves in this project. We dedicate this work to all of them and to the immunocompromised patients whom we hope this book will serve.

Randall T. Hayden, Karen C. Carroll, Yi-Wei Tang, and Donna M. Wolk
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