SECOND EDITION

URINARY TRACT INFECTIONS
MOLECULAR PATHOGENESIS AND CLINICAL MANAGEMENT
To the memories of Walter Stamm, MD and Carleen Collins, PhD and to the courage of Richard Grady, MD and Laura Hart, MD
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Urinary tract infection (UTI), the second most common infection of humans after pneumonia, has likely plagued the population for as long as humans have walked the face of the earth. The inception of antibiotics provided adequate therapy but did not prevent infections from recurring. While symptoms of the infections were well documented, little was known about the primary infecting pathogen, *Escherichia coli*. In 1976, Svanborg and colleagues demonstrated that *E. coli* causing acute pyelonephritis adhered in greater numbers to uroepithelial cells (1). Further research by several groups revealed that the adherence factor P fimbria was responsible. This structure was found to be comprised of a multi-protein complex with the actual adhesin placed at the tip of the fimbria. With the advent of molecular techniques, other advances arrived quickly. For example, in 1981, Welch and colleagues demonstrated that a knock out of the hemolysin gene attenuated *E. coli* in an intraperitoneal model (2). As discoveries abounded, some 14 years later, I teamed up with infectious diseases physician John W. Warren to edit a 15-chapter book titled *Urinary Tract Infections: Molecular Pathogenesis and Clinical Management*. This treatise covered the clinical aspect of UTI (5 chapters) and the molecular mechanisms of bacterial pathogenesis of UTI (10 chapters).

Now two decades have passed, and it was essential to update this broad topic. Editors Matthew A. Mulvey, David J. Klumpp, and Ann E. Stapleton have taken on the task of a second edition. The editors assembled an all-star lineup to cover the topic of clinical aspects of UTIs in eight chapters that include the anatomical and physiological aspects of UTI, clinical presentations, diagnosis and treatment, infections in children, involvement of the vaginal microbiome, asymptomatic UTI, prostatitis, pyelonephritis, and urosepsis (the most serious complication). In the second section (12 chapters), experts deal with reservoirs of infection, antimicrobial resistance, phylogeny, virulence, and fitness factors including exotoxins, structure of adhesins, adaptive mutations, and intracellular persistence, and this section includes chapters on other important uropathogens: *Proteus mirabilis*, *Klebsiella pneumoniae*, and Gram-positive pathogens. In the final section on host responses to UTI and emerging therapeutics (4 chapters), authors summarize the host response to UTI, innate immunity, sensation and pain in the bladder, and drug and vaccine development. Overall, this volume brings us up to date on the broad topic of UTI. Those interested in these common infections, whether it be in the laboratory or the clinic, will find the second
edition of *Urinary Tract Infections: Molecular Pathogenesis and Clinical Management* an indispensable book that should be on your shelf or on your computer. It is gratifying to see this critical topic brought up to date.

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Preface

For centuries the pain and other symptoms associated with urinary tract infections (UTIs) were erroneously ascribed to the wrath of gods, bile, phlegm, bad air, or numerous other culprits. The treatments for UTIs were at times equally off-target and included the use of bleeding and enemas, while the administration of narcotics and certain herbs provided palliative support. In the late 1800s, as evidence for the germ theory of disease mounted in the wake of Pasteur and Koch, the idea that microbes were responsible for UTIs took hold. This led to the development of more efficacious treatment options, culminating in the discovery and optimization of antibiotics that continue to this day. These achievements coincided with stunning advancements in our understanding of cellular functions and developmental processes within the urinary tract, inflammatory responses, microbiology, and the roles of both innate and adaptive host defenses. Still, despite this progress, UTIs continue to rank among the most common of infectious diseases, with most UTIs being attributable to strains of uropathogenic Escherichia coli (UPEC).

In 1996, for the first edition of this book, Harry L. T. Mobley and John W. Warren assembled an all-star cast of authors to highlight the multiple host and bacterial factors that impact the pathogenesis and treatment of UTIs. A lot has happened since, including remarkable progress in our ability to sequence and manipulate both bacterial and host genomes. The first *E. coli* genome, belonging to the nonpathogenic strain MG1655, was sequenced in 1997, followed a few years later by the urosepsis isolate and reference UPEC strain CFT073. Today, several thousand *E. coli* genomes have been sequenced, including many UPEC isolates. These data have revealed a huge amount of diversity among UPEC isolates, while also shedding light on the evolution and adaptability of uropathogens. These developments overlapped with the adoption of new, more facile approaches to manipulate UPEC genomes, greatly enhancing our ability to disrupt and functionally test specific pathogen-associated loci. This work is providing leads for the generation of more efficacious therapeutics for the treatment and prevention of UTIs.

Though powerful, antibiotics have not provided a cure-all for UTIs. Many individuals endure multiple recurrent UTIs despite antibiotic treatments, while circumstances such as catheterization render others prone to chronic infections. Many UPEC isolates are now resistant to multiple antibiotics, including some drugs that should be reserved as last resort choices. In terms of medical costs and loss of life, the rapid emergence and expansion of multidrug-resistant UPEC and related strains in recent years is considered by some to be more problem-
atic than methicillin-resistant *Staphylococcus aureus* (MRSA) was over the past two decades. The rising tide of antibiotic-resistant UPEC strains is showing no signs of subsiding, being driven in part by the overuse and misuse of antibiotics in both the clinic and in agriculture. Epidemiology informed by sequencing data is showing how antibiotic resistance and other genetic elements move among UPEC strains, facilitated by human activities such as global travel and the utilization of high-throughput animal processing and food distribution networks. To better combat UTIs, and antibiotic-resistant strains in particular, scientists are working to create effective anti-UTI vaccines and new antibiotics that have fewer off-target effects. Some researchers are optimizing the use of probiotic bacterial strains that can interfere with UPEC colonization of the urinary tract, while others aim to develop antivirulence strategies that modify virulence mechanisms and host responses rather than the bacteria themselves. The realization that UPEC can act as facultative intracellular pathogens in both humans and mice is also spurring the development of new treatment approaches while at the same time challenging long-held views concerning the etiology of chronic and recurrent UTIs.

Advances in bacterial genomics have been complemented by the development of new approaches to identify UTI susceptibility factors in human populations. This work, coupled with robust UTI model systems, is beginning to explain why some individuals are more prone to UTIs, making links with innate host defense regulators, adaptive immunity, inflammatory responses, and pain perception within the urinary tract. Clinically, we are gaining a much more complete understanding of the host and bacterial factors that contribute to the onset and progression of UTIs, as well as variables that can confound treatments. These variables include patient age, sex, and catheterization, as well as the makeup of protective microbial communities within the vaginal microbiota, the gut, and potentially even the bladder itself.

In this book, leading experts have reviewed the clinical diagnostics and management of UTIs in adults and children, along with associated complications such as urosepsis and prostatitis. In other chapters we take a detailed look at the origins of UPEC and associated antibiotic-resistance factors, with consideration of bacterial population dynamics, genome architecture, and evolution. The mechanisms by which uropathogens colonize the urinary tract and cause disease are thoroughly examined, with analysis of the adhesive organelles and myriad other bacterial and host factors that affect UPEC survival and virulence within the urinary tract. This includes an assessment of innate and adaptive host responses that are triggered during the course of a UTI, and the protective effects of microbial communities within the urogenital tract. The molecular biology and clinical importance of other uropathogens, including *Klebsiella pneumoniae*, *Proteus mirabilis*, and Gram-positive opportunists such as *S. aureus*, are also discussed in detail. Finally, we turn our attention to emerging antibacterial therapeutics, including the use of probiotics and bacterial interference measures. Much of the information presented in the following pages builds on work that was just coming to light when the first edition of this book was published nearly 2 decades ago. We are eager to see where the next 20 years take the field and hope that this new book, like the first edition, serves as both a resource for the community and a stimulus for future research endeavors.

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