Correspondence

Persistence of Intracellular Bacteria in the Urinary Bladder

TO THE EDITOR—We read with interest the review by Barber et al on urinary tract infections (UTIs) [1]. In general, we agree with the points made in the article. However, we wish to add a word of caution to the section on “recurrent UTIs and intracellular bacterial reservoirs” and some of the conclusions that may be drawn from this section.

Mulvey and colleagues and other groups have performed extensive and elegant in vitro and in vivo studies on UTI in a mouse model. These studies demonstrated the ability of uropathogenic Escherichia coli (UPEC) to survive inside of bladder cells and then emerge [2-5]. In the current article, this phenomenon is postulated to explain many of the delayed recurrences (>50% by some estimates) of lower tract infection. The section, in fact, seems to imply that the phenomenon does occur in humans. It is stated that experimental models (ie, mice) indicate that these quiescent intracellular UPEC reservoirs can persist for long periods in the absence of any overt clinical symptoms. This raises the question, what clinical symptoms might one expect in mice, and what are long periods compared to the human situation? The referenced experiments were of relatively short duration in terms of duration of follow-up.

While the animal studies are of interest, there is little or no evidence to support the phenomena of long-term intracellular persistence with relapse in humans. Residence in bladder cells has been demonstrated during acute cystitis but not long-term asymptomatic persistence or relapse [6]. Although the phenomenon may well turn out to be the case, it is premature to accept it as fact, or to act on it in terms of approach to therapy or prophylaxis except in controlled clinical investigations.

Note

Potential conflicts of interest. Both authors: No reported conflicts.
Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Reply to Kaye and Sobel

TO THE EDITOR—In their letter [1], Kaye and Sobel express concern regarding the model described in our recent review [2] in which we suggest that recurrent urinary tract infections (UTIs) may in part be attributable to the ability of uropathogenic Escherichia coli (UPEC) to invade and persist within the bladder epithelium. This idea is based on results from numerous studies dating back to 1998 that used bladder cell cultures and mouse models of UTI [3]. In mice, persistent bacterial populations within the bladder are often intracellular, as assessed by gentamicin protection assays and microscopy, and unfazed by antibiotic treatments that effectively sterilize the urine.

Ongoing studies in our lab and published work using mice indicate that these intracellular bacteria can reemerge sporadically and grow to high titers within the bladder lumen days to weeks after the cessation of antibiotic treatments (eg, [4–6]). The statement in our review that UPEC can persist intracellularly within the bladders of mice “without any overt clinical symptoms” was not the best choice of words and was perhaps too anthropomorphic [2]. We simply meant that mice could harbor intracellular UPEC reservoirs without displaying any obvious signs of inflammation and in the absence of any detectable bacteria within the urine.

Epidemiological studies support the possibility that intracellular bacterial reservoirs within the urinary tract are responsible for many recurrent UTIs in women, but these data may also be explained by the persistence of UPEC reservoirs within local environments outside of the urinary tract (discussed in [7]). Ex vivo assays show that UPEC can invade
human urothelial cells in tissue explants from volunteers, and the analysis of shed human urothelial cells collected from the urine of women with UTI symptoms indicates the presence of intracellular E. coli [8,9]. Together, these sorts of observations suggest that intracellular UPEC reservoirs are likely more than a mouse-specific laboratory phenomenon. However, Kaye and Sobel are correct in noting that the ability of UPEC to persist long-term intracellularly within the human urinary tract has not been established. Determining if intracellular UPEC reservoirs contribute to recurrent UTIs within the human population is a daunting task, plagued by issues of tissue procurement and contamination, possible reinoculation of the bladder by UPEC from niches outside of the urinary tract, and limited means to accurately detect small numbers of bacteria within a relatively enormous tissue. Ultimately, defining the relevance of intracellular UPEC reservoirs to the etiology of recurrent UTIs may only come to light with the development of approaches that can eradicate the reservoirs. We of course agree with Kaye and Sobel that it is premature to alter treatment protocols for recurrent or chronic UTIs outside of controlled clinical investigations based solely on results from mice, but we also feel that it is important to consider alternate rational explanations for recalcitrant UTIs, whether or not they gibe with the traditional view that UPEC act as strictly extracellular pathogens.

Notes

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Internet-Based Institutional Antimicrobial Stewardship Program Resources in Leading US Academic Medical Centers

TO THE EDITOR—We read with great interest the article by Moodley et al [1], which presents a review of infectious diseases applications (apps) for the iPhone/iPad and Android devices. The authors detail numerous resources and discuss potential opportunities to optimize app reliability or standardization, which is of value to a wide range of specialists. The purpose of this letter is to elaborate on the theme of accessible electronic resources by providing data on Internet-based institutional antimicrobial stewardship program (ASP) web pages from leading American academic medical centers.

We utilized online search engines to analyze hospitals listed as University Health-System Consortium (UHC) members [2] to identify the existence of hospital and health-system ASP web pages. UHC is an alliance of hospitals representing the nation’s leading academic medical centers. Existence and components of institution-specific ASP online resources were recorded. To identify potentially prototypical formats, an internet site was considered “comprehensive” when a clear program description accompanied resources for at least 3 ASP elements or strategies per the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America ASP guidelines [3]. Resulting data were evaluated and are presented using descriptive statistics.

The UHC member list produced 407 hospitals for evaluation. Of these, 24 (6%) were found to have online ASP resources through 18 unique websites. The Midwest and South US regions each account for a third of the websites. The median hospital size with an ASP website is just over 600 beds (range, 25–1550 beds). The Ohio State University Medical Center (Wexner Medical Center; http://rx.medctr.ohiostate.edu/as/) incorporates password restriction and The University of Chicago Medicine utilizes the social media website Facebook as a vehicle for their ASP website. A general program description and contact information are provided by 13 (72%) and 14 (78%) sites, respectively. A list of ASP members is available on 13 (72%) sites, with 15 (83%) sites disclosing both pharmacist and physician involvement. An antibiogram and external hyperlinks related to antimicrobial use are

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