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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References


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...