BACTERIAL PATHOGENESIS

The enemy within...

Despite appropriate therapy and follow-up, women who develop a urinary-tract infection (UTI) have a 44% chance of experiencing a recurrence within 1 year of the initial infectious episode. Reporting in *PLoS Medicine*, and extending their work using animal models, David Rosen, Scott Hultgren and colleagues provide evidence for the presence of intracellular bacterial niches in the urinary bladder of patients who have a UTI, a finding that has important implications for the recurrence of these infections and their treatment.

UTIs are primarily caused by uropathogenic *Escherichia coli* (UPEC), occur in approximately 13 million women per year in the United States and are responsible for substantial economic costs and associated morbidity. It was proposed that most recurrent infections are caused by the persistence of UPEC strains from the initial infection in the faecal flora, which were thought to return to, and reinfect, the bladder. Recent work on mice, however, suggested an additional explanation for UPEC persistence and recurrent UTIs. In this model, UPEC strains invade the epithelial cells that line the bladder and form intracellular bacterial communities (IBCs). Some infected epithelial cells are expelled into the urine, whereas others release bacteria, many of which adopt a filamentous morphology. These filamentous bacteria can resist the host immune response and, ultimately, the pathogen establishes an intracellular reservoir that

An immunofluorescent image of *Escherichia coli* (green) from the urine of a patient with a urinary-tract infection that shows a filamentous bacterium adjacent to several morphologically normal bacteria. Image kindly provided by David A. Rosen, Washington University School of Medicine, Missouri, USA. The scale bar represents 20 μ m.

is protected from both antibiotics and host immune surveillance.

To investigate the relevance of this animal model to human UTIs, Rosen *et al.* collected urine samples from 80 women who had acute uncomplicated cystitis (inflammation of the bladder) and 20 asymptomatic patients who had a history of UTI. Using a combination of light microscopy, electron microscopy and immunofluorescence, the authors detected IBCs in 18% of patients who presented with cystitis. Filamentous bacteria were observed in 41% of patient samples analysed, including all those patients who had detectable IBCs in their urine. The asymptomatic patient group, and those patients who were infected with Gram-positive pathogens, had no filamentous bacteria or IBCs. The authors were also able to show that all patients with evidence of IBCs, and most of those with filamentous bacteria in their urine, were infected with *E. coli*.

The data presented in this study provide strong evidence of an association between IBCs, filamentous bacteria and acute uncomplicated cystitis. This work also suggests that the IBC infectious cycle that is observed in the murine cystitis model is relevant, at least in part, to the human disease. Future work will include an analysis of urine samples taken at different time-points to assess the precise role of IBCs in UTI recurrence, and an investigation of whether UTI patients that present with IBCs might benefit from longer courses of antimicrobial agents or from agents that penetrate the intracellular space.

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ORIGINAL RESEARCH PAPER Rosen, D. A. *et al.* Detection of intracellular bacterial communities in human urinary tract infection. *PLoS Med.* **4**, e329 (2007)

FURTHER READING

Mysorekar, I. U. & Hultgren, S. J. Mechanisms of uropathogenic *Escherichia coli* persistence and eradication from the urinary tract. *Proc. Natl Acad. Sci. USA* **103**, 14170–14175 (2006)