

revealed chronic cystitis in 96 women, and follicular cystitis in three women (93%). The next year, the same group evaluated microbiological culture of homogenized bladder biopsies from 156 women with refractory OAB, of whom 38% had a history of recurrent bacterial cystitis. Bacteria were cultured from bladder biopsies in 52% of patients, most of whom had sterile CSU specimens on the day; a wide range of microbes were found including some fastidious organisms.³³

COVERT UTI IN PATIENTS WITH OTHER LUTD

At the same time as the above studies of refractory DO from Sydney and London, a further group in London approached the problem by looking at a broader group of patients with new-onset urgency/nocturia and other LUTD (without dysuria). Khasriya et al.³⁴ compared the diagnosis of bacterial cystitis in 470 CSU specimens, using the classical threshold (10^5 per ml) and the low count threshold (10^2 per ml), which revealed cystitis rates of 15% versus 29%, respectively. These authors concluded that use of the "classical" threshold for UTI diagnosis in patients with non-dysuric LUTD was of concern. The same group¹³ investigated women with chronic "urgency" associated with other LUTD, compared to controls, and showed that CSU specimens revealed a wide array of organisms causing bacteriuria at the 10^2 diagnostic threshold in the LUTD group. Further comparison of MSU versus CSU samples was provided³⁴ by these authors.

Recently, a group from Philadelphia established that premenopausal women with recurrent UTIs develop increased bladder sensitivity and signs of DO.⁸ In this urodynamic study, women with a history of recurrent UTIs were tested on a day when their urine culture was negative. These women were experiencing increased urinary frequency, reduced voided volumes and a lower threshold of bladder sensitivity in comparison with control subjects (who had stress incontinence with no history of UTIs). These results suggest that women with recurrent UTIs may have covert infection of the LUT and/or low count bacteriuria, between clinical infections, which contribute to the development of OAB symptoms.

PATHOPHYSIOLOGICAL MECHANISMS WHEREBY BACTERIAL CYSTITIS MIGHT PROVOKE OAB/DO

The majority of all human UTIs are caused by uropathogenic *Escherichia coli* (UPEC) strains, responsible for about 85% of cases.³⁵ Other pathogens commonly leading to acute cystitis include *Staphylococcus saprophyticus*, *Klebsiella* species, *Proteus mirabilis*, and *Enterococcus faecalis*.³⁶ The mechanisms whereby UPEC can establish chronic bacterial cystitis in the bladder wall have been well characterized using mouse models.^{19,37} *E. coli* strains enter the urinary bladder via the urethra and invade the bladder epithelium where they face a formidable array of host defenses including the production of antimicrobial factors (e.g., nitric oxide, defensins) and activation of immune cells (e.g., mast cells, macrophages). Despite these various host defenses, significant numbers of bacteria can reside within the bladder tissue for days to months by forming intracellular bacterial communities (IBC).¹⁹ These bacterial communities serve as a resource for covert and recurrent UTIs due to the flux of bacteria out of the host cells back into the lumen of the bladder, where they can invade naïve epithelial cells again.³⁸ In addition to forming IBCs, UPEC can enter a dormant state after trafficking into membrane-bound compartments that become enmeshed within host actin filaments forming quiescent intracellular reservoirs.³⁹ Animal models indicate that these quiescent intracellular UPEC can persist for long periods of time in the absence of overt clinical symptoms.²³ The intracellular localization of these bacteria renders them resistant to water soluble antibiotics and inaccessible to infiltrating neutrophils and other host defenses.^{22,40} The presence of bacteria within bladder wall is associated with number of structural and functional changes which could lead to the development of OAB. First, bacteria get access to (what and utilize nutrients necessary for normal physiologic function of the host tissue. Second, intracellular bacterial communities produce toxins and other metabolites which are released into intracellular spaces inside the bladder wall. These substances may affect the function of the urothelium as well as irritate sensory endings coursing in the bladder wall, thereby, triggering urgency and increased voiding frequency characteristic of OAB.

NEUROGENIC CYSTITIS, COVERT INFECTION AND DETRUSOR OVERACTIVITY IN ANIMAL MODELS

Among the factors initiating the occurrence of covert bladder infection, the role of viruses and antigen-induced inflammatory of the human urinary bladder is unknown. It is possible that viral invasion of the urothelium may precede bacterial infection and suppress the immune defense mechanism. However, no studies have been designed, to date, to test the hypothesis. Experimental injection of modified pseudorabies virus into the abductor caudae dorsalis tail muscle of the rat was shown to cause the occurrence of hemorrhagic cystitis.⁴³ Denervation of predominantly neural pathways in the process.⁴³ The observed neurogenic cystitis was accompanied by the release of pro-inflammatory and nociceptive substances by mast cells in the lamina propria of the bladder and resulted in pain, inflammation, and loss of barrier function of the urothelium.^{44,45} Further analysis detected the virus only in the spinal cord and brainstem, not in the urinary bladder or urine.^{43,46} These results suggest that future studies are required to clarify whether initial challenge of the nervous and immune systems with viruses could facilitate bacterial invasion into the bladder wall, thereby contributing to the occurrence of covert and persistent UTIs.

CLINICAL ATTEMPTS TO DEFINE INTRACELLULAR BACTERIA IN HUMANS WITH REFRACTORY DO AND OTHER LUTD

Most of the currently active research groups in this field have presented their attempts to demonstrate the presence of intracellular bacteria in patients with refractory IDO and other LUTD, with some preliminary evidence accumulating. Chen et al.⁹ employed confocal microscopy and saponin lysis of cells and revealed evidence of bacterial growth in 56% of samples that were negative on routine microbiology. Khasriya et al.¹⁰ showed that lysed urothelial cells were associated with increased detection of bacteria. The same group determined that isolates of bacteriuria from humans were capable of infecting bladder epithelial cells from a transitional cell carcinoma.¹² Horsley et al.⁴⁸ used uroplakin antibody stains for urothelial cell membranes with DAPI stains for microbial DNA as preliminary evidence of urothelial cells associated with bacteriuria. Further studies in this field are presently ongoing. Urinary tract infections have been well controlled by antibiotic regimens in the past. Several antibacterial drugs are

THERAPEUTIC AND PROPHYLACTIC CONSIDERATIONS FOR COVERT UTI