available for the treatment of acute bacterial cystitis including nitrofurantoin, trimethoprim/sulfamethoxazole, and fluoroquinolones (e.g., ciprofloxacin, levofloxacin), which are very effective in reducing bacterial titers in the urine (reviewed in Ref.[49]). However, frequent use of antibiotics for the treatment and prevention of UTIs triggered the evolution of antibiotic resistant microorganisms.[22,50,51] Therefore, novel therapeutic and prophylactic strategies are required to target IBC and quiescent bacterial reservoirs within bladder wall. These approaches should result in the development of drugs capable of crossing the plasma membrane to enter the infected cells. Since the majority of existing antibiotics are water-soluble, the need for novel membrane permeable drugs is very high.

Among prophylactic strategies, the use of cranberry products has been of research interest. At the bacterial level, cranberry juice compounds, as well as urine from mice fed cranberry juice, decrease the adhesion of UPEC to urothelial cells.[52,53] In vitro studies of human vaginal epithelial cells also showed an anti-adhesive effect of cranberry.[54] Nevertheless, two recent meta-analyses of several cranberry trials determined that cranberry products only have a slight protective effect, if any, against UTIs in humans.[55,56] Whether cranberry products can effectively treat or prevent UTIs still requires additional studies in order to draw definite conclusions on their use.

Several investigations have been conducted in attempts to create a vaccine against UTIs using UPEC cell lysates, FimH, FdeC and PapG adhesins, and flagellum components as antigens (reviewed in Ref.[57]). While these vaccines showed protection from UPEC colonization of the bladder and kidney in rodents,[58–61] and cynomolgus monkeys,[62,63] the pilot human studies revealed limited success. It is likely that vaccines which include combined antigens could be the most effective in preventing bacterial infection in humans. The collaborative efforts of specialists in genomics, bacteriology, and the human microbiome are required in order to develop effective treatment strategies for covert UTIs.

NEED FOR A RANDOMIZED CONTROLLED TRIAL OF ANTIBIOTIC THERAPY IN REFRACTORY DETRUSOR OVERACTIVITY

In the last 3 years, there have been two preliminary studies of antiobiotic therapy in patients with OAB. In 2011, researchers from University College published an abstract in which 147 patients with OAB and pyuria were treated with nitrofurantoin or cephalexin combined with antimuscarinic drugs and bladder training. For comparison, 212 patients with OAB, but without pyuria, who had received standard therapy (antimuscarinics and bladder training), over 7 years, were studied. The prevalence of traditional cystitis on MSU was 25% versus 12% respectively. The response to treatment (voids per 24 hr) was significantly greater in the antibiotic group versus standard treatment group ($P < 0.001$), but this was not a randomized controlled trial.[11] Few microbiological details of patients' urine samples were provided. Arising from the previously mentioned bladder biopsy study of Digesu et al.,[10] these same authors recently published a study of 39 women with refractory IDO and biopsy-evidence of chronic cystitis, who were given a 6 week course of rotating antibiotics (ciprofloxacin, doxycycline, cephalexin, modified according to patient allergies). This treatment yielded a significant reduction in voiding frequency, urgency scores, quality of life tests (all $P < 0.05$) as well as reduction in urinary nerve growth factor.[16] Again, no microbiological details regarding the persistence or cure of bacterial cystitis were given in this open prospective study.

FUTURE DIRECTIONS IN CLINICAL AND TRANSLATIONAL RESEARCH

Covert infection of the LUT may underlie bladder dysfunctions including OAB and DO. At present, the molecular mechanisms which allow maintenance of covert infection and inflammation of the human urinary bladder are still under investigation. The Think Tank participants discussed currently used clinical and basic science/translation approaches and also identified the main directions for future research including the following issues:

- The potential role of genetic differences underlying the individual response to infection among animal species and in humans has yet to be established;
- The role of autoimmunity in OAB/DO associated with covert infection is currently unclear;
- The ability of UPEC strains to reside in the bladder tissue for long periods of time suggests a need for sensitive assays for detection of covert bacterial infection in the clinical setting;
- Collaborative research between microbiologists, virologists and immunologists is warranted to achieve progress in the development of methods for detection and screening of preexisting covert bacteriuria, as well as for the discoveries of antibiotics capable of clearing bacteria from the bladder tissue;
- The importance of designing and conducting an adequately powered randomized controlled trial of antibiotic treatment, with microbiological results as an important outcome measure, was emphasized during discussion. Outcome measures should be analyzed as to the relation between cessation of bacteriuria and the amelioration of OAB symptoms. In summary, we may be at a crossroads, where interest in the role of covert infection in the genesis of refractory detrusor overactivity and other LUTS can only be sustained by the establishment of a clear methodology framework and well-defined terminology, that will facilitate future research.

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