Infection and Inflammation of the Genitourinary Tract

Re: Clinical Validation of Integrated Nucleic Acid and Protein Detection on an Electrochemical Biosensor Array for Urinary Tract Infection Diagnosis

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Background: Urinary tract infection (UTI) is a common infection that poses a substantial healthcare burden, yet its definitive diagnosis can be challenging. There is a need for a rapid, sensitive and reliable analytical method that could allow early detection of UTI and reduce unnecessary antibiotics. Pathogen identification along with quantitative detection of lactoferrin, a measure of pyuria, may provide useful information towards the overall diagnosis of UTI. Here, we report an integrated biosensor platform capable of simultaneous pathogen identification and detection of urinary biomarker that could aid the effectiveness of the treatment and clinical management. Methodology/principal Findings: The integrated pathogen 16S rRNA and host lactoferrin detection using the biosensor array was performed on 113 clinical urine samples collected from patients at risk for complicated UTI. For pathogen detection, the biosensor used sandwich hybridization of capture and detector oligonucleotides to the target analyte, bacterial 16S rRNA. For detection of the protein biomarker, the biosensor used an analogous electrochemical sandwich assay based on capture and detector antibodies. For this assay, a set of oligonucleotide probes optimized for hybridization at 37°C to facilitate integration with the immunoassay was developed. This probe set targeted common uropathogens including E. coli, P. mirabilis, P. aeruginosa and Enterococcus spp. as well as less common uropathogens including Serratia, Providencia, Morganella and Staphylococcus spp. The biosensor assay for pathogen detection had a specificity of 97% and a sensitivity of 89%. A significant correlation was found between LTF concentration measured by the biosensor and WBC and leukocyte esterase ($p < 0.001$ for both). Conclusion/significance: We successfully demonstrate simultaneous detection of nucleic acid and host immune marker on a single biosensor array in clinical samples. This platform can be used for multiplexed detection of nucleic acid and protein as the next generation of urinary tract infection diagnostics.

Editorial Comment: Urinary tract infections remain a common and costly source of health care costs in the United States and abroad. In the past these infections have been treated with empirical antibiotics with good results. However, as we have seen during the last 10 years, resistant organisms are emerging that are making empirical treatment of urinary tract infections less effective. Point of care testing that could first identify a urinary tract infection and also identify the appropriate type of antibiotic required to treat the infection would be incredibly useful.

These authors have been pursuing a point of care biosensor based assay for urinary tract infections for several years now. In this publication they report modifications to their biosensor, which allows them to better identify uropathogens and also identify the presence of white blood cells in the urine specimen. Their platform can sense these organisms and white cells in about 1 hour. These data are exciting and push the field forward. The next step will be to develop a biosensor that looks for pathogenic islands in these organisms as well as genetic markers of drug resistance. With this tool one

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could first identify the organism and secondarily understand potential sensitivities and resistance patterns.

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Re: Chicken as Reservoir for Extraintestinal Pathogenic Escherichia coli in Humans, Canada

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We previously described how retail meat, particularly chicken, might be a reservoir for extraintestinal pathogenic Escherichia coli (ExPEC) causing urinary tract infections (UTIs) in humans. To rule out retail beef and pork as potential reservoirs, we tested 320 additional E. coli isolates from these meats. Isolates from beef and pork were significantly less likely than those from chicken to be genetically related to isolates from humans with UTIs. We then tested whether the reservoir for ExPEC in humans could be food animals themselves by comparing geographically and temporally matched E. coli isolates from 475 humans with UTIs and from cecal contents of 349 slaughtered animals. We found genetic similarities between E. coli from animals in abattoirs, principally chickens, and ExPEC causing UTIs in humans. ExPEC transmission from food animals could be responsible for human infections, and chickens are the most probable reservoir.

Editorial Comment: Extraintestinal E. coli are a leading cause of community acquired urinary tract infections in humans. It has traditionally been thought that these E. coli originate in the host intestinal tract and then migrate into vaginal and urinary systems, where they persist and cause infections. Recently advances in genetic testing have identified cluster outbreaks of urinary tract infections caused by genetically identical strains of E. coli, which suggests these E. coli may also exist in other reservoirs. This research group has studied the sources for these outbreaks.

In this report the authors describe genetic similarities between E. coli isolates obtained from retail meat and extraintestinal E. coli in humans that are known to have caused community acquired urinary tract infections. Here they examined E. coli isolates from raw chicken, beef and pork products as well as E. coli isolates from the cecum of beef cattle, chickens and pigs. They compared these E. coli isolates to geographically and temporally matched E. coli isolates from humans who had urinary tract infections. The retail meat containing isolates that most closely resembled E. coli from humans with urinary tract infections was chicken. Retail beef and pork had isolates that were less similar to uropathogenic E. coli but were much less common than isolates from chicken. Next, the investigators linked several E. coli clones from food animals and demonstrated that these isolates were similar to pathogenic E. coli isolated from people with UTIs.

In summary, extraintestinal uropathogenic E. coli can be derived from food sources and food animal reservoirs. Moving forward, this issue will be an important consideration when regulators begin to think about what type of antibiotics our food sources (chickens, cows and pigs) can be safely exposed to.

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