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IMPROVING THE DIAGNOSIS OF URINARY TRACT INFECTION IN OAB

Hypothesis / aims of study

In recent times the view that urinary tract infection (UTI) might be playing a substantial role in the aetiology of overactive bladder (OAB) has been voiced. This hypothesis originally grew from publications from different centres casting doubts on the veracity of routine urine cultures (1). If the screening tests used to assess OAB patients lack sensitivity, we should not be complacent over whether infection has been excluded from this condition.

Much of the current evidence for unidentified UTI in OAB has rested on indirect markers of infection or inflammation. Data from microbial isolation studies has been limited (2). It is widely accepted that routine midstream urine (MSU) culture, using the traditional Kass criteria of 10^5 cfu ml^{-1}, is inadequate and an alternative is needed. To be clinically useful, a novel culture method should be suitable for MSU sampling, and capable of achieving rapid results.

Experiments reported in recent years have demonstrated that urine infection appears to arise from the intracellular colonisation of urothelial cells by pathogenic bacteria. It appears that the pathogens have evolved extremely sophisticated mechanisms for achieving this.
The urothelium responds to bacterial invasion by mounting an innate immune response. An important element in this reaction is the shedding of urothelial cells and increased cell production through hyperplastic transformation. These elements co-operate to generate increased numbers of urothelial cells in the urine and a significant proportion of these should be colonised by pathogenic bacteria.

This motivates the hypothesis that culture of the urothelial cell concentrates, prepared by centrifuge, should provide a suitable substrate for the culture of pathogenic bacteria from ordinary urine samples. Encouraging data have been described but from methods which included use of Columbia blood agar (CBA), were laborious and required CSU sampling (3).

Chromogenic agar (CPS3), unlike CBA, allows immediate identification of bacteria. This study tested the hypothesis that culture of the urinary spun sediment, collected from MSU samples, using CPS3 agar would differentiate between OAB patients and controls. The experiment first compared the CPS3 and CBA methods. Next the CPS3 method was tested on MSU samples from patients and controls to check for the all-important properties of disease discrimination and variation related to disease severity.

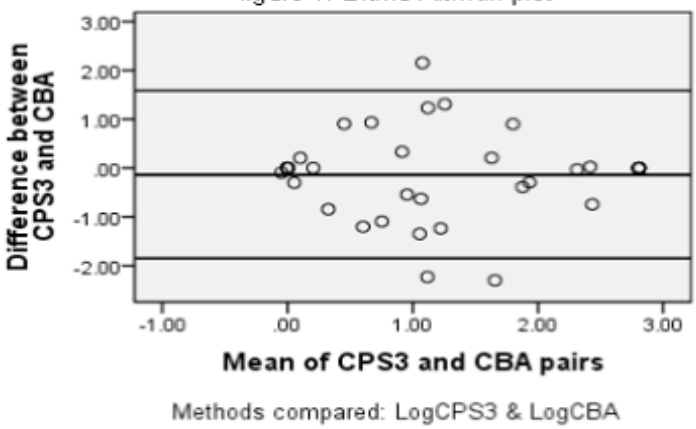
Study design, materials and methods

Meticulous MSU specimens were obtained from 24 female OAB patients at varied treatment stages and 8 controls. Cell sediment was extracted by centrifuge at 2000rpm for 5 minutes and resuspended in sterile phosphate buffered saline solution. 50 ul aliquots were inoculated onto CPS3 and CBA plates. Analytical profile index (API) tests were used to confirm the bacterial species. A separate experiment of 52 subjects and 18 controls analysed data on sediment cultures to compare bacterial growth in differing clinical states, OAB with pyuria, OAB without pyuria and control subjects. A post-hoc calculation confirmed that this study had greater than 80% power to detect a significant between group difference (α=0.05).

Results

In experiment 1, all 8 controls were negative for both routine urine culture (< 10^5 cfu/ml) and sediment culture (zero cfu/ml). 8 out of 24 (33%) of the patients showed a positive routine culture; 19 out of 24 (79%) of the patients had a positive sediment culture on both CPS3 and CBA plates (mean = 10^2 cfu/ml). A Bland-Altman plot (figure 1) was used to measure the agreement in the log transformed colony counts of the bacterial isolates identified on the CPS3 and CBA plates, for all 24 OAB patients. The plot displayed very good agreement between the two methods.

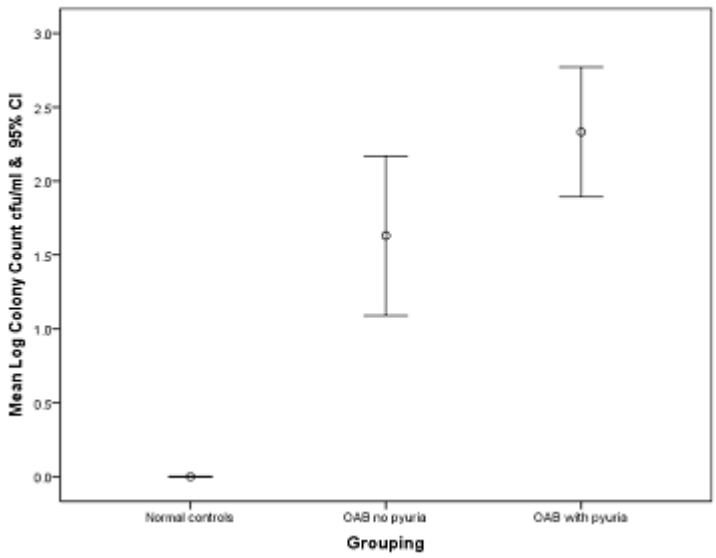
figure 1: Bland-Altman plot



In experiment 2, there were 52 OAB patients and 18 controls. 29 (55.6%) of the OAB patients exhibited pyuria; 23 (44.2%) did not have pyuria. All 18 controls revealed a negative sediment culture. 43 (82.7%) of the OAB patients grew a positive sediment

culture and the mean total log bacterial colony count varied significantly between the different clinical states (figure 2). The non-parametric Kruskal-Wallis test confirmed a significant difference in mean total log bacterial colony counts in patients with OAB pyuria, OAB no pyuria and controls.

figure 2: Mean log colony count across different clinical states



Interpretation of results

Test agreements cannot be measured by correlation or comparisons of means. The Bland-Altman plot (aka Tukey mean-difference plot) is a well-validated method. The good agreement observed between CPS3 and CBA methods justifies chromogenic agar as a replacement of blood agar for the sediment culture. The significant differences, in mean log total colony, across the disease spectrum, imply a discriminatory power of potentially considerable clinical value.

Concluding message

These studies provide microbiological evidence of an active infective pathology in OAB. They also demonstrate a novel approach to urine culture based on a modern appreciation of the pathophysiology. These data seem to presage an advance in clinical diagnostic methods.

References

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Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**This work was conducted with approval from the Whittington and Moorefield's Research Ethical Committee, London**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**