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Mini Review

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Steps Toward Prevention and Treatment of Female UTI Using PDT

Alison M Mackay*

Faculty of Medicine, Biology and Health, University of Manchester, Oxford Road, Manchester, UK

***Corresponding author:** Alison M Mackey, Faculty of Medicine, Biology and Health, University of Manchester, Oxford Road, Manchester, UK.

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Abbreviations: ESKAPE: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter Baumanni, Pseudomonas Aeruginosa, and Enterobacter species; FI: Faecal Incontinence; LED: Light Emitting Diode; PDT: Photodynamic Therapy; ROS: Reactive Oxygen Species; rUTI: Recurrent UTI; UI: Urinary Incontinence; UTI: Urinary Tract Infection; uUTI: Uncomplicated human UTI

Introduction

Recent research on skin infection and its treatment with PDT identified combinations of photosensitisers and light for eradication of specific pathogens [1]. It has also been discovered that both the Photosensitiser Drug (PS) and the action of Reactive Oxygen Species (ROS) are subject to microbial tolerance gradually over time [2]. However, this resistance is likely to develop more slowly than antibiotic resistance, which is a serious issue for those with recurrent infections caused by ESKAPE pathogens [3]. Using multidisciplinary knowledge of physics, urology and microbiology, a logical next step would be to apply PDT to the treatment of UTI [4], identification of the pathogen in-situ as a guide for the choice of PS and light wavelength by imaging is an aspirational and longer-term endpoint. The aim of this study is to collate information on the incidence and nature of Urinary Tract Infection (UTI) in females, and to consider treatments based on clinical, translational and lab research.

Study Design, Materials and Methods

Literature Review.

Results

Epidemiology

The opening chapter of the seventh International Consultation on Incontinence [5] describes the incidence of Urinary Incontinence (UI) and Faecal Incontinence (FI) as a function of health, maternal, and social factors. However Urinary Tract Infection (UTI) was omitted. Women are significantly more likely to experience UTI than men [6], and their lifetime incidence of UTIs is reported to be 50-60%, with prevalence increasing with age [7]. Among a cohort of 113 young women with UTI, 27% percent experienced at least one recurrence (rUTI) within six months [8]. Catheter-associated UTI is the most common nosocomial infection, accounting for over a million cases at any one time in US hospitals and nursing homes [9].

Microbiology

Uncomplicated Human Urinary Tract Infection (uUTI) is caused by *Escherichia coli* [10], however *E. Faecalis* and *Staphylococcus saprophyticus* have also been found [11]. In catheter users, the Klebsiella and Proteus genera are present in the urine. In those with diabetes mellitus, *Klebsiella*, *Enterobacter* and *candida genera* are likely, with *Enterococcus spp* and *candida spp* also reported in complicated human UTI.

Technology

GaniteTM is a Gallium Nitrate preparation proven to destroy biofilm-forming urinary pathogens in the lab [12] including a variety of *E. Coli* and *P. Aeruginosa* Strains. This research group have a patent for the intravesical instillation of the drug in humans

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and so clinical trial data is imminent. In rats a Foley catheter with an embedded fibre optic light guide delivered a photosensitiser and laser irradiation synergistically [13] demonstrating that the technology works, even at a small scale. More realistically for an ambulant animal, a wireless LED device was implanted in a mouse given oral 5-Aminovulenic acid. This treated lab-induced cancer over several days and is known as metronomic Photodynamic Therapy (PDT)[14].

The optimal light and photosensitiser combinations for PDT of a variety of human infections have been published [1]. For example, methylene blue and 660nm light is thought to kill Covid-19. PDT can kill microbes even if they are resistant to antibiotics, and any tolerance that the pathogens develop is likely to happen slowly. The technique was recently employed in conjunction with antibiotics to treat UTI caused by e-coli [15]. Lothar Lilge at al. [16] describe the intravesical instillation of a photosensitiser and fibre-optic delivery of green light during PDT for bladder cancer. The shape of the bladder, optical properties of the mucosal layer, and the geometry of illumination all influenced treatment efficacy. Castle and co-authors [17] describe the use of PDT, infrared laser therapy and bacterial interference in a cohort of patients with Neurogenic bladders and rUTI.

Interpretation of Results

The technology to deliver PDT to bladders already exists but should be evaluated for human females with symptomatic UTI. Effective parameters are known for skin infection [10]; however, they may require alteration for intravesical use necessitating further clinical research.

The simple treatment method of instilling a drug into to bladder is protected by at least one patent and so alternative versions may have to be researched. However, the use of antibiotics with adjunctive pharmacy is emerging could halt the development of microbial resistance, suggesting they will remain a useful method of treatment in some situations.

The research chapter of ICI consultation seven outlines the need for prevention and early intervention in UTI [18]. The Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium aims to expand research beyond the detection and treatment of Lower Urinary Tract Symptoms (LUTS) to the promotion and preservation of bladder health and prevention of LUTS in girls and women [19]. PDT has successfully prevented skin cancers [20] , and so over time an application for rUTI and related LUTs may emerge.

Concluding Message

Several techniques are being developed for the treatment of infection to avoid overuse of antibiotics and the emergence of resistant microbes. PDT appears close to being ready for clinical use in UTI and may have roles in treatment and prevention.

Acknowledgement

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Conflict of Interest

None.

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