Advances in Colloid and Interface Science 249 (2017) 53–65

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

journal homepage: www.elsevier.com/locate/cis

Historical perspective

Emerging nanotechnology based strategies for diagnosis and therapeutics of urinary tract infections: A review

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ARTICLE INFO

Keywords:
Urinary tract infections
Nanotechnology
Nanoparticles
Antimicrobials
Diagnosis
Biosensor
Nanoantibiotics

ABSTRACT

At present, various diagnostic and therapeutic approaches are available for urinary tract infections. But, still the quest for development of more rapid, accurate and reliable approach is an unending process. The pathogens, especially uropathogens are adapting to new environments and antibiotics day by day rapidly. Therefore, urinary tract infections are evolving as hectic and difficult to eradicate, increasing the economic burden to the society. The technological advances should be able to compete the adaptability characteristics of microorganisms to combat their growth in new environments and thereby preventing their infections. Nanotechnology is at present an extensively developing area of immense scientific interest since it has diverse potential applications in biomedical field. Nanotechnology may be combined with cellular therapy approaches to overcome the limitations caused by conventional therapeutics. Nanoantibiotics and drug delivery using nanotechnology are currently growing areas of research in biomedical field. Recently, various categories of antibacterial nanoparticles and nanocarriers for drug delivery have shown their potential in the treatment of infectious diseases. Nanoparticles, compared to conventional antibiotics, are more beneficial in terms of decreasing toxicity, prevailing over resistance and lessening costs. Nanoparticles present long term therapeutic effects since they are retained in body for relatively longer periods. This review focuses on recent advances in the field of nanotechnology, principally emphasizing diagnostics and therapeutics of urinary tract infections.

1. Introduction

Infectious diseases topped the list of leading death causes at the beginning of 20th century. Urinary tract infections (UTIs) refer to the presence of microbial infection within urinary tract and classified by the site of infection as cystitis, pyelonephritis and prostatitis. There was no proper widely accepted definition for recurrent urinary tract infections (RUTIs) until 2000 [1]. Then after, many publications on RUTI defined as three or more episodes of UTI in the last twelve months [2,3]. Some publications defined as UTI relapsing two or more times in last six months [4,5]. UTIs are one of the most neglected but common infections, estimated to be nearly quarter of the entire healthcare associated infections. The incidence and severity vary with age, sex and several genetic susceptibility factors. The uropathogens are common all over the world. Both Gram positive and Gram negative have the potential of causing UTIs. Most commonly, Gram negative uropathogenic bacteria include *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *K. oxytoca*, *Salmonella paratyphi*, *Citrobacter freundii*, *Vibrio cholera*, *Serratia marcescens*, *Providencia stuartii*. Enterobacteriaceae constituted more than 80% of the reported cases, of which *E. coli* is the most common pathogen in community acquired as well as catheter associated UTIs [6].

One of the recent technological advances to concentrate on this problem is to explore nanoparticles, against which the pathogens may not develop resistance. Nanotechnology is at present an extensively developing area of immense scientific interest since it has diverse potential applications in biomedical field. Nanotechnology may be combined with cellular therapy approaches to overcome the limitations caused by conventional therapeutics. Colloidal zinc oxide nanoparticles were shown to exhibit antibacterial properties against a broad range of

Abbreviations: UTI, urinary tract infection; RUTI, recurrent urinary tract infection; UPEC, uropathogenic *Escherichia coli*; CDC, Centers for Disease Control and Prevention; NHANES, National Health And Nutrition Examination Survey; NIDDK, National Institute of Diabetes, Digestive and Kidney Diseases; ED, emergency department; CNF, cytotoxic necrotising factor; IBC, intracellular bacterial communities; QIR, quiescent intracellular reservoirs; TMP-SMX, trimethoprim-sulfamethoxazole; IMC, isothermal microcalorimetry; CFU, colony forming units; FTIR, Fourier-Transform Infrared spectroscopy; UVRR, UV Resonance Raman spectroscopy; SERS, Surface Enhanced Raman Spectroscopy; MALDI-TOF, Matrix Assisted Laser Desorption Ionization Time-of-Flight; MS, mass spectrometry; PCR, polymerase chain reaction; rRNA, ribosomal ribonucleic acid; ELISA, enzyme linked immunosorbent assay; Ig, immunoglobulin; LAL, limulus amebocytes lysate; LPS, lipopolysaccharide; SPR, surface plasmon resonance; NP, nanoparticles; UV, ultraviolet; PPE, paraphenyleneethynylene; GNP, gold nanoparticles; PECA, poly(ethyl-2-cyanoacrylate); PAMAM, polyamidoamine; TEM, transmission electron microscope; ROS, reactive oxygen species

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http://dx.doi.org/10.1016/j.cis.2017.06.010
Received 30 January 2017; Received in revised form 23 June 2017; Accepted 23 June 2017
Available online 26 June 2017

pathogens [7,8]. Zinc oxide nanoparticles offered higher bactericidal activity against *Staphylococcus aureus* compared to other metal oxide nanoparticles [9]. Gold nanorods were employed for specific targeting towards pathogenic microorganisms and destroying them by the use of phytothermal treatment [10]. Gold nanoparticles are higher photostable, lesser toxic, easily attuned to surface modifications compared to silver. Moreover, gold nanoparticles could be modified so that they can absorb near infrared radiations, which could be transferred to the attached bacterial cells in the form of heat and result in irreversible cellular damage [10].

2. Urinary tract infections (UTI)

2.1. Etiology and epidemiology of UTI

UTIs comprise about 13% of the total healthcare associated infections, reported with an estimated number of 93,300 infections annually [11]. It is estimated that more than 1 million patients join hospitals due to catheter associated UTIs, the most common nosocomial infection. As per the reports by the Centers for Disease Control and Prevention (CDC), UTIs account for 13,000 deaths annually, with a mortality rate of 2.3% and it may be increased to 10% if UTIs are associated with bacteremia. 15–48% death rate had been reported in the patients suffering from proteus bacteraemia and 35% of the nosocomial infections reported are due to UTIs [12], and the prevalence of UTIs increases with age [13] and also with the increase in duration of catheterization [14]. Of the patients infected with UTIs in the hospitals, 50% would have a chance of recurrence in the next sixty days. UTI stands among the major three prevalent infections in India [15] and are the most common bacterial infections in infants and children [16]. According to previous studies, 50% of women will suffer from UTI at least once during their lifetime; 10–20% of women experience each year, 1–2% of women encounter with frequent recurrences [17] and 50% of women suffering from asymptomatic bacteriuria are thought to develop pyelonephritis [18]. High morbidity and long term complications like chronic renal failure are associated with pediatric urinary tract infections [19]. A connection between UTI and diabetes mellitus had been identified earlier in the 1940s and urinary tract had been reported as the major site of infection in diabetic patients [20]. UTIs are more frequent in diabetic patients as hyperglycemic urine stimulates bacterial growth and colonization [21]. UTIs are the most common type of infections during pregnancy where cystitis can be rapidly transformed into pyelonephritis [22]. According to NHANES (National Health And Nutrition Examination Survey) and NIDDK (National Institute of Diabetes, Digestive and Kidney Diseases), during 1988–1994 in US, approximately 6.2 million adults or 2.28% had reported suffering from cystitis for more than 3 months. According to Hospital Episode Statistics, Department of Health, England, 0.096% of hospital visits were associated with cystitis in England during 2002–03, 97% of which required hospital admission. Cystitis is estimated to affect 10/100,000 of the Finland population. Approximately 8.2% of the people are estimated to be suffering from prostatitis [23].

The overall hospital mortality rate due to severe sepsis was 28.6%, which represents 215,000 deaths nationally. Patients with preexisting medical conditions would experience higher mortality rates. The mortality rate due to acute pyelonephritis is higher when associated with early clinical failure and the important issues for rapid clinical failure are chronic liver diseases, diabetes mellitus, and malignancy [24]. 15–17 cases were reported per 10,000 populations in the United States and 80% of cases were women [25].

2.2. UTI related healthcare costs

The health care costs can be directly correlated to the economic burden of that specific disease. The economic burden of a disease is the total price of the resources used or lost by the patients, organization and the society due to that disease. It includes direct costs (such as diagnosis and treatment costs), indirect costs (such as the salary lost by the patients, productivity lost by the organization and mortality costs) and impalpable costs (such as costs of suffering). The exact economic burden may be difficult to determine. The total health care costs can be separated into the following five groups: physician visits, inpatient hospitalizations, outpatient visits, emergency department visits and drugs associated with the disease [26].

The total costs for UTIs were thought to be $2.14 billion in 2000 and approximately $2.9 billion in 2013. It has been reported that 15% of the antibiotics prescribed in the USA are for UTIs, the cost of which exceeds $1 billion annually. A study conducted on 1118 emergency department (ED) patients and 41,605 outpatients reported that the mean pharmacy costs were $2971 and $1882 for ED patients and outpatients respectively during the full treatment period [27]. In the UK more than 320,000 patients develop UTIs each year, which results in more than £900 million cost. The Agency for Healthcare Research and Quality reported that sepsis is the most costly disease in U.S. hospitals, with more than $20 billion in 2011.

2.3. Virulence factors

Genetic and immune factors of the host as well as virulence factors of pathogens contribute to UTI. Specific virulence factors residing on uropathogenic *E. coli* membrane play a significant role in attachment to the host cells, colonization, infection, and resistance mechanisms. Adhesins present on the surface of the bacterial membrane act as specific recognition molecules and aid in the initial attachment or adherence of bacteria to uroepithelial cells. The capacity of adherence is the main characteristic of pyelonephritogenic strains of *E. coli* [28]. TolC protein, an outer membrane protein has a role of transferring the α-hemolysin toxin out of the *E. coli* outer membrane [29]. α-hemolysin mediates pore formation on erythrocytes, leukocytes, endothelial cells and renal epithelial cells. Cytotoxic necrotising factor1 (CNF-1) may be involved in polymorphonuclear phagocytosis and apoptosis of uroepithelial cells. Some strains of uropathogens express *S*-fimbriae, the binding sites of which are present on epithelial cells of glomerulus, proximal and distal convoluted tubules and collecting ducts in kidney. Cytolysin secreted by *Enterococcus faecalis* enhances its virulence and is associated with higher mortality. Human erythrocytes are susceptible to cytolysin mediated hemolysis [30]. Endotoxins, also known as lipopolysaccharides present in the outer wall of Gram negative uropathogens are considered to be the main causative agents of the UTIs. Endotoxins are composed of mainly three regions: O-specific antigen which is the main recognition site for the cells of immune system, core polysaccharide and lipid A [31]. Endotoxins induce inflammatory responses when they come in contact with the cells of immune system such as monocytes and macrophages and stimulate these cells to release mediators such as tumor necrosis factor and interleukins and produce free radicals [32]. High concentrations of endotoxins result in overwhelming immune responses that may lead to septic shock [33].

2.4. Biofilm formation

A bacterial biofilm is defined as a three dimensional structured group of cells with complex interactions present in an auto-produced polysaccharide matrix that is capable of adhering to both abiotic and biotic surfaces and characterized by genetic diversity and structural heterogeneity [34,35]. Bacterial biofilms are associated with the severity of a large number of chronic infections. Biofilm producing bacteria are resistant to disinfectants and sanitizers [36], antibiotics, host immune defenses and other stresses [37], that makes it difficult in eradicating the associated infections [38]. Biofilms provide a nutrient rich environment that promotes survival and growth of uropathogenic *E. coli* (UPEC), and protects from antimicrobial drugs [39].