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Risk Factors Associated with the Development of Multi Drug Resistant Uropathogenic Bacterial Strains

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Abstract: Urinary tract infections (UTIs) are one of the most prominent infections reported globally. The emergence of multi drug resistance (MDR) is one of the key threats in the health care system worldwide. Identifying the risk factors for multidrug-resistant urinary tract infections is very much essential to combat the public health threat. The development of MDR among UTIs is now increasing in an alarming pace. It necessitates the importance of identifying the risk factors associated with the development of MDR among UTI pathogens. In this review we are summarizing the major risk factors allied with MDR in UTI. It will show limelight into the management strategies to minimize the development of new MDR strains which is essential for the well being of the human race.

Key words: Extended Spectrum Betalactamases · Multi Drug Resistance · Urinary Tract Infections

INTRODUCTION

The evolution of multi drug resistance (MDR) among pathogens is a public health threat all over the world. The pathogens are acquiring new resistance mechanisms in a terrifying pace which intensifies the failure of standard treatment to common infectious diseases. As a result, it will cause prolonged illness, higher treatment cost and enormous risk of mortality. In the entire infectious agents (Bacteria, Fungi, Virusess and Parasites), the evolution of MDR is an expected trend. Even though, the indiscriminate use of antimicrobial drugs, insufficient sanitary conditions, unsuitable food handling methods and poor infection prevention and control measures contribute to emergence of and push the further spread of MDR. Urinary tract infections (UTIs) are the most frequently reported infections and force the antibiotic use around the world [1, 2]. UTIs are the fourth most common type of healthcare-associated infection [3]. Due to the higher rate of occurrence and the increased use of antibiotic the rate of emergence of MRD among uropathogens are more frequent. The drug resistant uropathogens are a severe threat to humans all over the world and a potential challenge to modern medicine. In case of immune compromised patients with HIV, severe diabetes, patients undergone organ transplantation, patients suffering from severe burns the risk of acquiring MDR uropathogens infection from hospitals are extremely high [3]. Therefore it is essential to identify the various factors that contribute to the development of MDR among uropathogens in order to mitigate the risk factors. In this review we are mainly focusing on various factors that may contribute to the development of MDR in uropathogens. This may help in reducing the emergence of MDR in UTI patients.

Significance of MDR among Uropathogens: Antimicrobial drugs are widely used all over the world for the management of urinary tract infections for several decades. The indiscriminate use of antibiotics among UTI patients led to the spread of MDR among uropathogens. International consensus defines multidrug resistance as non-susceptibility to at least one antimicrobial in three or more classes, based on in vitro susceptibility testing [4]. Extensively drug-resistant (XDR) organisms are defined as isolates with susceptibility to only one or two antimicrobial classes, with resistance to agents in all remaining categories. Pan-drug resistance is resistance to all antimicrobials in all the classes [4]. The worldwide spread of multidrug-resistant pathogens has led to a

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boost in UTIs even in children that are complicated to treat [5]. The studies depicted that at least 7% of the children will experience a UTI by the age of 19 years [6]. MDR uropathogens are becoming more and more prevalent in both community-acquired infections and hospital-acquired infections, though prevalence varies by region [7]. All these depicted the necessity of identifying the root causes behind the emergence of MDR in uropathogens.

Problems Associated with MDR: The main problem associated with MDR in uropathogens is increased mortality rates. It also causes prolonged treatment time, increased financial burden and reduces the overall effectiveness of the antimicrobial agent. The prolonged infectious state in patients may increase the risk of further spread of MDR pathogens and causes obstacles in the management of the disease. Many of the MDR uropathogens are resistant to the common commercially available antibiotics. So we have to switch to alternative expensive antibiotics for the treatment. Other present day medical practices such as organ transplantation and cancer chemotherapy are also found to be associated with the spread of MDR uropathogens [35]. Another factor triggering the world wide spread of the MDR pathogens are the global trade and tourism.

Classification of MDR: The clinical failure of an antimicrobial drug is associated with several factors other than multi drug resistance. Immune compromised state of the patient, poor or deprived bioavailability of the drug and increased rate of drug metabolism are some among them [13]. MDR can be classified mainly into primary and secondary.

Primary Resistance: Primary resistance occurs when the pathogen have never exposed to the drug of concern in a particular host [8].

Secondary Resistance: Secondary resistance occurs only when a pathogen has exposure to a drug of concern. It is also known as acquired resistance. It can be further classified into intrinsic and extensive resistance [9]. Intrinsic resistance (MDR) refers to the insensitivity of all microorganisms of a single species to certain general first-line drugs, which are used to treat diseases based on the clinical proof of the patient. Extensive resistance (XDR) defines the capability of organisms to survive the inhibitory effects of at least one or two most efficient antimicrobial drugs. In addition to the above mentioned classes, clinical resistance may also occur. The pathogen is inhibited by an antimicrobial concentration that is higher than could be safely achieved with normal dosing [9].

Mechanisms of MDR in Uropathogens: The vast majority of the UTIs are reported by the members of the family Enterobacterales (Gram negative). Among them more than 80% of the cases are associated with *Escherichia coli* [10].The other Gram negative bacteria were found to be associated with UTIs are *Klebsiella* spp., *Enterobacter* spp. and *Proteus* spp. Rarely Gram negative organisms for instance *Pseudomonas aeruginosa* may cause UTIs. The possible Gram positive bacteria associated with UTI in adults as well as in children were *Enterococcus* spp. and *Staphylococcus saprophyticus* [11].

There are various mechanisms of antimicrobial resistance in bacteria. The most common method found in Enterobacterales is the production of betalactamases [12]. Betalactamases can be classified in many ways. The Ambler classification system is based on the molecular structure of the enzymes while Bush-Jacoby classification, is based on functional characteristics [13]. The ambler classification of betalactamases is summarized in Table 1.

The ESBLs were first originated by a single nucleotide polymorphism (SNP) in the *blaSHV* gene and studies showed that surplus of 1600 ESBLs are now circulating worldwide [15]. Most of the ESBLs genes are observed to be associated with plasmids [16]. The plasmid mediated resistance is more important in the context of public health, since it can easily transfer from one species to another via horizontal gene transfer mechanism. Moreover, ESBL producing bacteria were more frequently MDR also. The plasmid associated with ESBL can carry other antimicrobial resistant genes such as aminoglycosides, fluoroquinolones and sulphonamides [17].

Risk Factors for MDR UTI: The major risk factors associated with MDR in UTI are previous history of antibiotic use, previous hospitalization and anomalies in the urinary tract. But community acquired MDR organism infections are also possible without any identifiable risk factors [18]. There is escalating proof that human movement facilitates the worldwide spread of resistant bacteria and antimicrobial resistance (AMR) genes. In one study, 290 individuals in Norway were identified with UTI

Table 1: Families of beta-lactamase enzymes:

Class	Enzyme	Example genes	Organisms affected	Detection and treatment
Ambler class A	ESBLs including CTX-M, SHV	blaCTX-M-15	*E. coli*	Inhibited by clavulanic acid
		blaCTX-M-27	*K. pneumoniae*	Remain susceptible to carbapenems
		blaCTX-M-14	*P. mirabilis*	Chromosomal genes may be inducible
	Carbapenemases KPC	blaKPC	*E. coli*	Inhibited by clavulanic acid
			K. pneumoniae	
			K. oxytoca	
			S. marcescens, *Enterobacter* spp.	
			C. freundii	
Ambler class B	Metallo-beta-lactamases,		*E. coli*	Remain prone to aztreonam
	including IMP, NDM		*K. pneumoniae*	NDM producers normally have
			K. oxytoca	extra resistance genes
			S. marcescens, *Enterobacter* spp.	
			C. freundii	
Ambler class C	Cephalosporinases AmpC	blaCMY-2	*Chromosomal* AmpC	Chromosomal or plasmid-mediated
			Enterobacter spp.	Chromosomal genes may be inducible
			C. freundii	Also resistant to aztreonam
			S. marcescens	Remain prone to
			M. morganii	•Carbapenems
			P. stuartii	•4th generation cephalosporins,
			Plasmid AmpC	e.g. cefepime
			K. pneumoniae	•Avibactam
			E. coli	
Ambler class D	Oxacillinases	blaOXA-23	*A. baumannii*	Highly diverse group of enzymes,
		blaOXA-48	*P. aeruginosa*	some also hydrolyse carbapenems
		blaOXA-1		

TEM named after the first patient Temoniera, SHV sulphydryl variable, CTX-M named as resistance to cefotaxime, ESBL extended spectrum beta-lactamases, KPC Klebsiella pneumoniae carbapenemase, MBL metallo-beta-lactamases, NDM New Delhi metallo-betalactamase [13]

caused by an extended spectrum β-lactamase-producing (ESBL) *Escherichia coli* or *Klebsiella pneumoniae*. On further investigation it was revealed that these infections are connected with their travel history to Asia, Africa or to Middle East [18]. Extra intestinal pathogenic *Escherichia coli* (ExPEC) are the most widespread root of community-acquired as well as hospital-acquired extra intestinal infections. It can be assumed that the human ExPEC may have an animal food reservoir which has been explored by several groups worldwide. Many researches depicted that the combined pathogenic potential of human ExPEC and avian pathogenic *E. coli* suggests that these extra intestinal *E. coli* may be raised from the identical bacterial lineages or may share common evolutionary roots. The explicit human ExPEC lineages were found only in poultry or poultry products and hardly ever in other meat products, braces the hypothesis that there may be a poultry reservoir for human ExPEC [19]. ExPEC constitutes ongoing health disquiet for women, infants, elderly and immune compromised individuals due to increased numbers of urinary tract infections (UTIs), newborn meningitis, abdominal sepsis and septicemia [20]. ExPEC strains cause considerable healthcare problems. These bacteria also infect chickens and cause a big loss to the poultry industry. To get around ExPEC-related expenses, antibiotics are frequently used in the poultry industry to put off/treat the microbial infections and support growth and performance. In an adverse relationship, chicken products are suspected to be a foundation of food borne ExPEC infections and antibiotic resistance in humans [20]. Thus it is evident that a division of all human ExPEC infections, especially antimicrobial-resistant ExPEC infections, can be attributed to the evolution of MDR ExPEC lineages through contaminated food product(s) [19].

One of the study depicted that the frequent consumption of poultry or poultry products is a major risk factor which causes UTI an AMR (resistance to 51 antimicrobial class) or MDR (resistance to 53 antimicrobial classes) *E. coli* [21]. The instantaneous source of the *E. coli* that grounds extra intestinal infections is normally the individual's own intestinal tract. While intestinal colonization does not lead to any direct ill effects, *E. coli* are available to cause disease when risk factors for an extra intestinal infection occur. For instance, the principal risk factor for UTI in young women is sexual intercourse.

The mechanics of sexual intercourse aid the transfer of intestinal *E. coli* from the anus, across the perineum to the urethra and bladder. Although food is one probable source, ExPEC have also been recognized in multiple nonhuman reservoirs, including companion animals, wastewater and other environmental sources [22].

Another risk factor connected with the development of UTI is liver cirrhosis (LC). Patients with liver cirrhosis (LC) have a distorted immune system that makes them susceptible to an extensive range of infections [23]. In patients with LC, healthcare-associated infections concerning multi-drug resistant (MDR) bacteria have amplified drastically over the previous decades. Among them, hospital-acquired urinary tract infections (HA-UTIs) are the most frequent. Another vulnerable group susceptible to UTI is children with spina bifida (SB) [24]. The study revealed that newborn (up to 18 months) with SB had generally a higher UTI infection rate with MDR organisms (21% vs. 10%, $p < 0.01$). The *E. coli* isolates from these subjects showed an increased rate of antibiotic resistance to various agents such as aminoglycosides, fluoroquinolones, cephalosporins, extended spectrum β-lactams and TMP-SMZ.

The prior use of ciprofloxacin and catheterization are two independent significant factors which are responsible for the development of ciprofloxacin resistant UTIs [25]. Impediment of infection due to multi-drug resistant organisms is difficult. The spreading of resistant bacteria usually occurs beyond the hospitals into the community as well as other secondary healthcare establishments like nursing homes [26]. Individual or demographic uniqueness that may affect risk of colonization of the urinary tract with MDROs include older age [27-29], female sex [27], a history of UTIs [30, 31] and diagnoses of dementia or poor functional level [23, 31], diabetes [28, 30] and prostatic disease. Predisposing or healthcare-associated factors connected with augmented risk of community acquired MDROs in the urinary tract comprise invasive procedures such as urinary catheterization [32], previous hospitalization [33], residence in a nursing home and prior contact to antimicrobials [32-34].

Urinary tract infection (UTI) positions among the most frequent infectious complications among kidney transplant recipients, with up to 79% prevalence [35]. Although kidney recipients are mostly at risk to MDR/XDR Gram-negative UTIs, which can lead to increased cost and longer extent of hospitalization, available data in this field among this population are limited [36, 37].

CONCLUSIONS

In this review we are summarizing the various risk factors allied with the advancement of MDR in UTI organisms. Identifying the risk factors is essential for the proper management of the MDR UTIs. Prior antibiotic use, age, sex, prior hospitalization, abnormalities in urinary tract, kidney transplantation, liver cirrhosis, sexual intercourse, immune-suppressive diseases etc are some of the major risk factors associated with the evolution and propagation of MDR UTIs.

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