Review Paper:

Review on Amikacin resistance in Uropathogens

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Abstract

Urinary tract infections (UTIs) represent frequently recorded bacterial infections worldwide, predominantly caused by Escherichia coli. Amikacin, an aminoglycoside antibiotic, has historically been proven therapeutic approach for severe UTIs, especially when resistance to other antibiotics is a concern. However, the emergence and spread of amikacin resistance in Uropathogenic Escherichia coli (UPEC) strains have raised significant clinical challenges. The amikacin resistance mechanisms in UTIs, mainly the molecular mechanisms behind resistance development, the prevalence and distribution of amikacin-resistant UPEC strains in different age groups also should be considered. Resistance to amikacin in UPEC often arises due to aminoglycoside-modifying enzymes, efflux pumps, or alterations in the bacterial ribosomal target sites. These resistance mechanisms may be intrinsic or procured through horizontal gene exchange, further complicating treatment options.

The prevalence of amikacin-resistant UPEC strains in UTIs is considerably increasing. Since Amikacin is the important and primary therapeutic option of various pathogenic UTIs including other multidrug resistance strains such as ESBL producers, the development of Amikacin resistance should be taken into account as a dangerous scenario.

Keywords: Urinary Tract Infection, Amikacin, Antibiotic Resistance, Uropathogenic strain of *Escherichia coli* (UPEC).

Introduction

The infection of urinary tract, including the urethra, bladder, ureter and kidneys constitutes urinary tract infection (UTI). Urinary tract is expected to be free of commensals, microorganisms that propagate in the urinary tract resulting in UTI's[44]. Boys in their infancy, elderly men and females of all age categories are particularly susceptible to UTI's. Frequent recurrences of UTI, sepsis related pyelonephritis leading to renal damage in young children, pre-term birth and complications caused by high-level antibiotic resistant uropathogens are serious concerns[19,20]. UTIs are divided into uncomplicated and complicated categories. Uncomplicated UTI is acute cystitis (Lower UTI) or pyelonephritis (Upper UTI) in a younger woman without structural or nervous system abnormalities in the urinary tract system.

Pyelonephritis or cystitis in males, children, chronically catheterized patients and women with recurrent UTI, urologic abnormalities or underlying disease is considered as complicated UTIs[31,40]. The microbial etiology includes both Gram-negative and Gram-positive bacteria as well as certain fungi. Escherichia coli (UPEC) is the predominant etiological agent responsible for both mild and severe UTIs. Other etiological agents responsible for uncomplicated UTIs, are Gram negative bacilli such as *Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa*, Gram positive cocci such as group B *Streptococcus* (GBS), *Enterococcus faecalis, Staphylococcus saprophyticus* and *Staphylococcus aureus* and fungus such as *Candida spp*[25,31,34].

The prevalent agents for complicated UTIs are *Uropathogenic isolates of Escherichia coli* (UPEC), preceeded by *Enterococcus spp., Klebsiella pneumoniae, Candida spp., Staphylococcus aureus, Proteus mirabilis, Pseudomonas aeruginosa* and group B *Streptococcus* (GBS)[20,25,38]. The most commonly recommended therapeutic agents for UTIs include trimethoprim, sulfamethoxazole, ciprofloxacin, amikacin and ampicillin[19]. Antibiotic resistance constitutes a serious challenge for health care professionals affecting the ability to determine appropriate first-line treatment modalities for urinary tract infection (UTI). Resistance rates to commonly used antibiotic agents may vary based on geographic region or country. Previous exposure to antimicrobial agents is a notable risk factor for acquiring antibiotic resistant genes during the first and recurrent UTI[20].

Aminoglycosides are a group of antibiotics primarily used to treat bacterial infections due to its broad spectrum activity[32]. Streptomycin, the first aminoglycoside, was discovered in early 1944 and is still in use[10,21]. This was followed by the discovery of neomycin (1949)[26] and kanamycin (1957)[20] and gentamicin[19]. With the continued use and exposure to natural aminoglycosides, the organisms acquire resistance mechanisms that challenge its use for therapy. Amikacin, a semisynthetic aminoglycoside was synthesized by acylation at the C-1 amino group of the deoxystreptamine moiety of kanamycin A[6] and was patented in 1971.

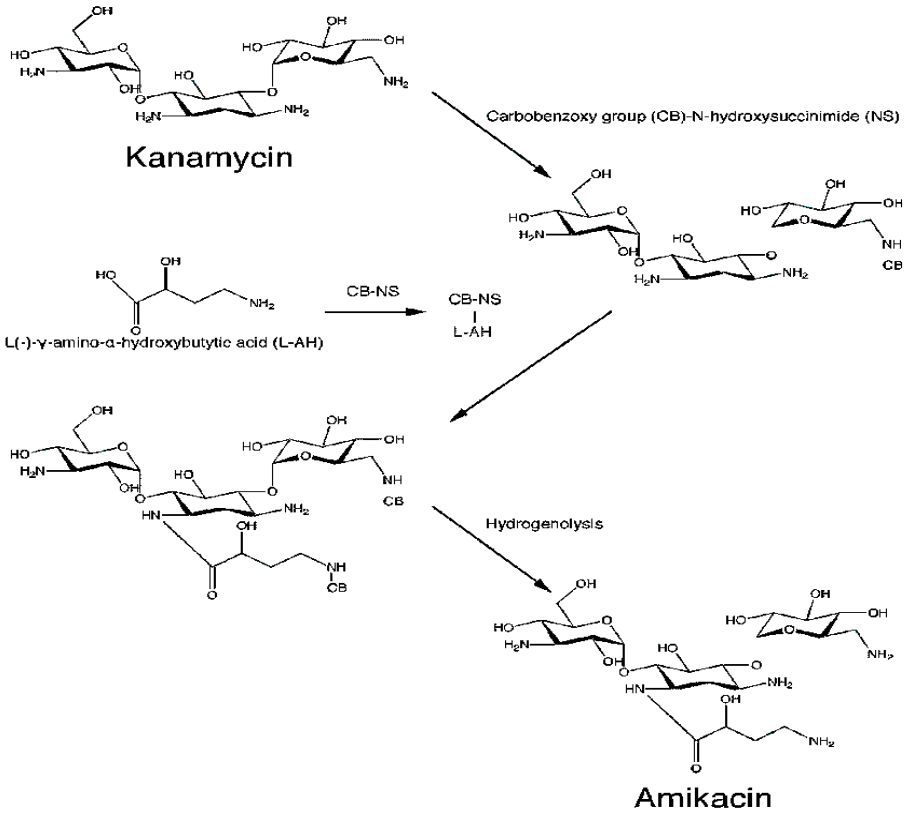

Figure 1: Schematic representation of Amikacin Synthesis from Kanamycin A[23].

Mechanism of Action of Amikacin: Amikacin is a widely used antibiotic as a management option for both uncomplicated and complex UTIs, even for infections with multidrug-resistant organisms. The dosing strategy of amikacin for UTI's is mostly weight-based and is divided into two to three applications per day with 8 to 12 h intervals. Aminoglycosides binds to the anionic compounds found on the surface of bacteria that are either Gram positive or Gram negative organisms because of their polycationic nature. Presence of lipopolysaccharide, phospholipids and outer membrane proteins in Gram-negative bacteria and teichoic acids and phospholipids in Gram-positive bacteria serves as substrates for drug interaction. This drug interaction increases permeability and results in the penetration of aminoglycoside molecules into the bacterial periplasmic space[23].

This is followed by entry of a limited number of antibiotic molecules into the cytoplasm with functional electron transport system, an energy-dependent process. After reaching the cytoplasm, the antibiotic proceeded with its activity[39,45]. Aminoglycosides acts by binding to the 30S bacterial ribosome subunit changing the conformation of the A site and resulting in reduced proof-reading capabilities of the ribosome[4].

Abnormal membrane proteins induce damages to cytoplasmic membrane integrity facilitating abundance of aminoglycoside molecules in the cell. The accumulation of aminoglycoside molecules within the bacterial cell results in high levels of protein synthesis errors leading to higher rate of uptake of the drug, eventually resulting in death of the cell[30,47]. When present at sub-inhibitory concentrations, aminoglycosides can also cause other disruptions to bacterial cells and can modify transcription rates[22]. At low concentrations, amikacin disrupts the formation of the Z ring leading to inhibition of cell division[43].

Resistance to Amikacin: Urinary tract infections (UTIs) caused by multidrug resistant strains particularly, extended-Spectrum beta-lactamase (ESBL)-producing bacteria have become a growing problem that limits therapeutic options. Resistance rates to amikacin in Gram negative bacteria tend to be low even among ESBL-producing isolates. Treatment of UTI's with amikacin independently or combined with other antibiotics is recommended[11]. Various mechanisms operate that aid to documented cases of amikacin resistance which comprise of chromosomal mutations and acquisition of plasmid-mediated genes that alter the enzymatic activity[25]. Currently among the aminoglycosides available for human use, amikacin is less prone to the action of aminoglycoside modifying enzymes[11,29].

Plasmid-mediated enzyme, acetyl transferase, known as AAC(6′)-Ib or AacA4[7,1], was first reported in *Pseudomonas aeruginosa* that conferred amikacin resistance. Previous studies have reported amikacin resistance due to plasmid mediated phosphotransferase enzyme and chromosomal in non-clinical *E. coli* strains[8,42]. A plasmid-mediated adenylyl transferase was reported in *Klebsiella pneumoniae, E. coli* and *Proteus vulgaris* strains that aid to amikacin resistance[46]. Among the variety of amikacin resistance mechanisms

identified in clinics, the main one is acetylation of the 6'-N position. The enzymes usually confer resistance to aminoglycosides such as amikacin, tobramycin and kanamycin but not the gentamicin complex[27].

The presence of AAC(6')-I enzymes is increasing rapidly in Gram-negative bacteria[27]. Despite various AAC(6′)-I identified in gram-negative bacteria, the AAC(6′)-Ib enzyme is mostly found in *Enterobacteriaceae* and *Pseudomonadaceae*[5]. The aac(6′)-Ib genes reside in plasmids, chromosomes, transposons, integrons and genomic islands[34,35]. Tn1331 is a transposon that encodes four resistance genes, one of them is aac(6')-Ib isolated from *K. pneumoniae*[28], this transposon and its derivatives are later found in various Gram-negatives bacteria plasmids[9,41]. In the case of Gram-positive organism, some 6'-N-acetyltransferases with the AAC(6'-I profile were found within the Tn4001-like transposons[18,33] which are identified in plasmids and chromosomes of Gram-positive bacteria such as *S.aureus, S.epidermidis* and *Enterococcus faecalis*[35,37].

Studies on widespread nature of Amikacin resistance encountered in Urinary Tract Infection reported that most of the etiological agents were sensitive to amikacin and gentamycin[13,17]. Various reports suggests that the most widespread causative agents of UTI's are *Escherichia coli* and *Klebsiella pneumoniae*, which are recognized as sensitive to amikacin. In the case of UTIs in children, the evidence from studies highlights that resistance rate to amikacin is continuously increasing with prior exposure to drug[12,15]. In a recent study analysis report, approximately 10% of *E.coli* were identified as resistant to amikacin. Amikacin can still be considered as the preferred drug for treatment of UTIs caused by *E. coli*[14,36].

Amikacin-Glimpse of hope for UTI therapy

The clinical management of UTIs has been hindered by increasing resistance rates to frequently used antibiotics reported worldwide. While choosing a treatment regimen, clinicians should consider the local susceptibility pattern, adverse effects, cost effectiveness and selection of resistant strains. Aminoglycosides are one of the most sought after antimicrobial agents among parenteral antibiotics for management of UTI. Because of high urinary excretion, aminoglycosides reach a concentration of 25-100 folds than that of serum. The capability of Amikacin monotherapy and combination therapy aimed for treating ESBL UTI.

Among multidrug resistant urinary isolates, low resistance (0-47%) to amikacin is observed worldwide when compared with cephalosporins and fluoroquinolone resistance. The main concerns utilizing aminoglycoside for UTI therapy are nephrotoxicity and ototoxicity. The threat of nephrotoxicity and ototoxicity is elevated in patients with impaired renal function and also in those with normal renal function who receive higher doses for extended time than those recommended. To combat risk associated with amikacin therapy, before administration of amikacin and at the end of treatment, patient's renal function need to be assessed.

Conclusion

The resistance rates to amikacin in most of the bacteria are generally low in both Gram negative and Gram positive strains. Urinary tract infections (UTIs) caused by multidrug resistant strains have arisen, a growing problem that limits therapeutic options. Treatment of UTIs with amikacin independently or combined with other antibiotics is recommended. Different mechanisms aid to amikacin resistance such as chromosomal mutations and acquisition of plasmid-mediated genes that alter the enzymatic activity. Studies report a high sensitivity level to amikacin in UTIs irrespective of age groups and genders.

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