

Antimicrobial Resistance: A Threat in Nephrology

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Abstract: Kidney diseases mainly include acute kidney injury, chronic kidney disease, glomerulonephritis, diabetic nephropathy, and urinary tract infections. Nephrology disease can lead to decline in patients own immune system, resulting in serious infections. Urinary tract infection is a common infection of nephrology disease, which causes a very serious impact on health of patients. Therefore, analysis of pathogen distribution should be strengthened. Infection is a major cause of morbidity at all stages of chronic kidney disease (CKD) and can directly contribute towards patient mortality. CKD patients may be at an increased risk of infection due to background impairment in host immunity. Therefore, infection prevention and management in the CKD population requires holistic care.

I. INTRODUCTION

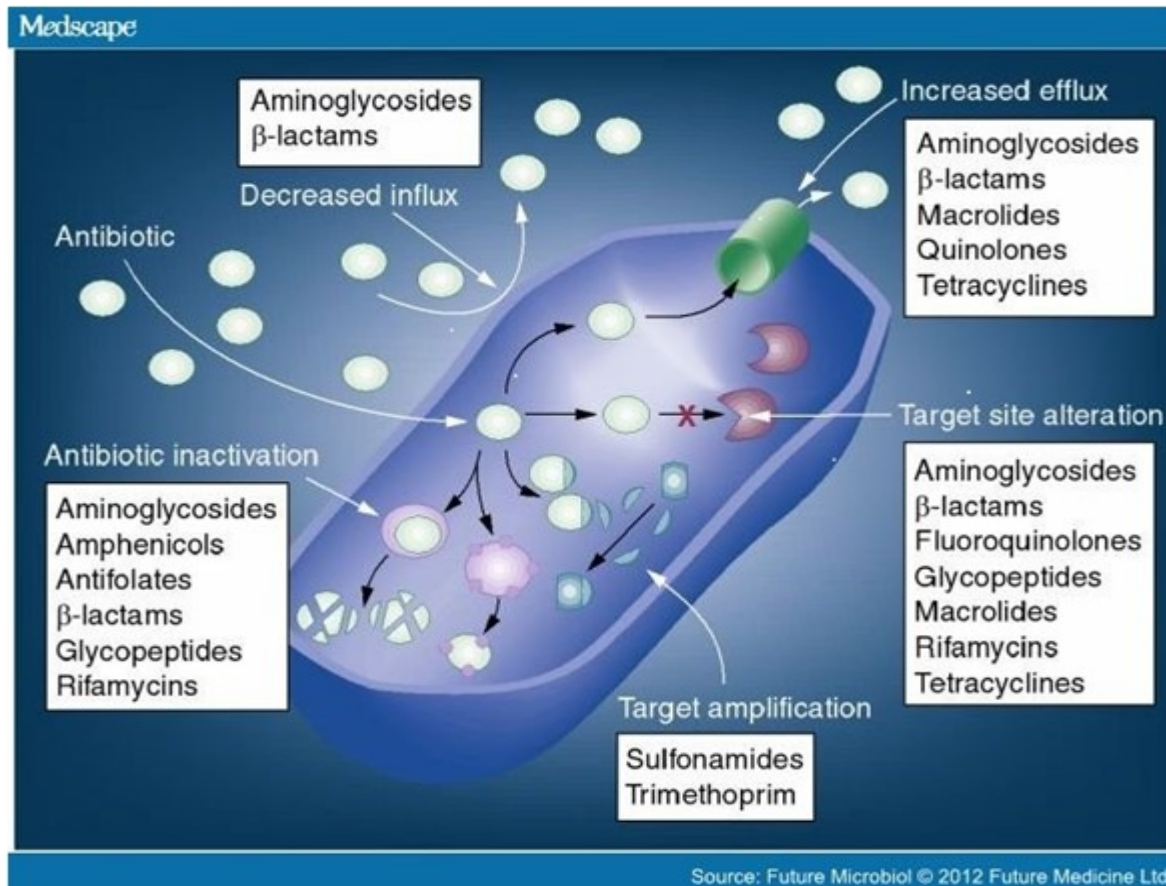
Antimicrobial resistance means a naturally susceptible microorganism acquires way of being not affected by the drug. It is not a new phenomenon. It is now accepted as a major problem in public health and patient care.

Understanding the mechanism of resistance is important in order to find better ways to keep the existing agent useful, and all so help to design better new antimicrobial. It is now well known that antimicrobial use is the single most important factor for the antimicrobial resistance^[1].

Mechanism of Resistance

Mechanisms of resistance mainly include decreased drug uptake, efflux pumps, enzyme inactivation and target alterations by mutation^[1].

- The inactivation or modification of antibiotics
- An alteration in the target site of the antibiotic that reduces its binding capacity
- The modification of metabolic pathways to circumvent the antibiotic effect
- The reduced intracellular antibiotic accumulation by decreasing permeability and or increasing active efflux of the antibiotics.



How to Reduce Antimicrobial Resistance?

- Prepare appropriate guidelines for the proper use of antibiotics in healthcare facilities.
- Implement antimicrobial stewardship program.
- Increase proper immunization coverage that may reduce the use of antibiotics.
- Reduce antimicrobial use for agricultural practice and animals.
- Create awareness among people on rational use of antibiotics.
- Establish strong policy for dispensing of antibiotics by vendors.
- Control Hospital and community acquired infections^[2].

II. RESISTANCE IN NEPHROLOGY

In nephrology diseases, mainly include acute kidney injury, glomerulonephritis, chronic kidney diseases, poly cystic kidney diseases and urinary tract infections. Out of this, resistance has mostly seen with chronic kidney disease population with renal failure. So analysis of pathogen distribution should be strengthened^[2]. Patients with CKD are victim of infection due to decline in patient’s own immune system, and also a reservoir of antibiotic-resistant pathogens. An increased risk of infection has been reported higher in CKD population undergoing hemodialysis. It results in frequent use of antibiotics and more frequent hospitalization^[3]

Uropathogens isolated

- E.coli
- Klebsella spp.
- Enterobacter spp.
- Multi-drug resistant organisms include methicillin resistant Staphylococcus aureus, vancomycin resistant Enterococci, and multi resistant gram negative^[4].

From a retrospective study conducted by Karimzadeh et.al, at a 20 bed adult nephrology ward of Nemazee hospital affiliated to Shiraz University of Medical Sciences, Iran. The 3 most common isolated gram-negative bacteria from all biological samples of patients were *Escherichia coli*, *Klebsiella* spp. and *Acinetobacter* spp. (15.4%). Most gram-negative bacteria were isolated from urine. The most frequent resistance was seen with cephalosporins including cephalexin (80-95.7%), cefixime (70.6%-89.2%), ceftriaxone (67.6%-94.9%), cefotaxime (70.4%-100%), and ceftazidime (75%- 100%). The 3 antibacterial agents with the lowest resistant rates were colistin (4.76%), amikacin (27.3%- 35 %), and chloramphenicol (41.2%-52.3%)^[5].

III. COMMONLY USED ANTIBIOTICS- CONSIDERATIONS IN CKD AND ESKD PATIENTS

In general antibiotics are categorized in to time-dependent or concentration dependent.

| Time- dependent antibiotics | Concentration- dependent antibiotics |
|--|--|
| Penicillins Cephalosporins Carbapenems Vancomycin Oxazolidinones Macrolides | Aminoglycosides Lipopeptides Fluroquinolones |

When dosing time-dependent antibiotics, it is important to maximize time>MIC, where as when dosing concentration-dependent antibiotics, the peak:MIC ratio is the most important to optimize^[6].

IV. MECHANISMS OF ANTIBIOTIC CLASSES

| Mechanism of action | Antibiotic class |
|-----------------------------------|---|
| Cell wall synthesis inhibitors | β -lactams, vancomycin, lipoglycopeptides (eg. telavancin, oritavancin) |
| DNA synthesis inhibitors | fluroquinolones |
| Protein synthesis inhibitors(50s) | Oxazolidinones (eg. linezolid, tedizolid) |
| Protein synthesis inhibitors(30s) | aminoglycosides |
| Folate synthesis inhibitors | Sulfamethoxazole-Trimethoprim |
| Cellular membrane dysfunction | Lipopeptides (eg. daptomycin) |

β -lactam antibiotics

Penicillins, cephalosporins, and carbapenem antibiotics all coming under this category . Their mechanism of action is through inhibition of last step in bacterial cell wall synthesis. Penicillins have antimicrobial activity against various gram positive organism like β -Hemolytic streptococci, Viridans streptococci, Streptococcus pneumonia, Enterococcus faecalis, Listeria monocytogenes, MSSA, etc . and various gram negative organisms like Haemophilus influenza, E.coli, Proteus mirabilis, Moraxella catarrhalis, Klebsella spp., bacteroides fragilis. Commonly treated infectious diseases using penicillins are pharyngitis, endocarditis, neurosyphilis, osteomyelitis, lower respiratory tract infections, genito-urinary tract infections, Prosthetic joint infections, Blood stream infections, Diabetic foot infections. β -lactams exhibit time-dependent pharmacodynamics, so proper dosage adjustment should be done in CKD population. When doses have not been adjusted properly, central nervous system disturbances such as confusion, myoclonus, seizures can occur^[6].

Aminoglycoside antibiotics

These are class of antibiotics have the mechanism through inhibition of bacterial protein synthesis. Amikacin, gentamicin, tobramycin are coming under this category. Aminoglycosides have retained activity against gram positive organisms like enterococcus spp., MSSA and gram negative organisms like Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenza, Moraxella catarrhalis. These are used to treat various infections like endocarditis, pneumonia (hospital-acquired or ventilator-associated), urinary tract

infections, pyelonephritis. Risk of oto- and nephrotoxicity are mostly associated with aminoglycosides^[6].

Fluoroquinolones

Ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin are coming under this class of antibiotics. They inhibit DNA synthesis through inhibition of DNA gyrase in gram negative bacteria and topoisomerase in gram positive bacteria. Commonly treated infections diseases are intra- abdominal infection, pneumonia (community acquired, hospital acquired), prostatitis, osteomyelitis. They have high oral bioavailability and excellent tissue penetration. Peripheral neuropathy, tendon rupture and CNS defects are some serious adverse effects. Drug interaction occurs between phosphate binders and fluoroquinolones, leads to decreased antibiotic absorption and treatment failure. So proper considerations should be there among CKD population^[6].

Vancomycin

Is a glycopeptide antibiotic, with mechanism of cell wall synthesis inhibition. It has activity against gram positive organisms like streptococci, MSSA/MRSA, Staphylococcus epidermidis, enterococcus faecalis, enterococcus faecium and limited activity against negative organisms. It is used to treat various infections like blood stream infections, clostridium difficile colitis, endocarditis, osteomyelitis, sepsis and septic shock, skin infections. Nephrotoxicity is a common concern of vancomycin, and it is associated with concurrent use of other nephrotoxic antibiotics (aminoglycosides)^[6].

Oxazolidinones

Are a new synthetic class of antibiotic with the mechanism of inhibition of protein synthesis. They have significant activity against gram positive pathogens such as Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Enterococcus faecalis and Enterococcus faecium. They also have activity against various multi-drug resistant pathogens such as methicillin-resistant staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), vancomycin-intermediate strains (VISA), and penicillin-resistant pneumococci (PRPN). Linezolid is the first compound in this category and is indicated for the treatment of both hospital and community acquired pneumonia and skin and skin structure infections^[7].

Lipopeptides

Cyclic lipopeptide antibiotics contain various kinds of amino acids. They exhibit a wide variety of biological activities such as antimicrobial, antifungal, antitumor, and enzyme inhibitory activities. Daptomycin, a fermentation product produced by Streptomyces roseosporus, is a cyclic lipopeptide with potent bactericidal activity against most gram positive organisms. The mechanism of action through cellular membrane dysfunction, causing rapid membrane depolarization and a potassium ion efflux and followed by arrest of DNA, RNA and protein synthesis leads to bacterial

cell death. Daptomycin is indicated to treat complicated skin and skin structure infections. It has activity against Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae subsp. Equimilis and Enterococcus faecalis^[8].

V. CONCLUSION

Antimicrobial resistance has rapidly evolved in the last few decades to become now one of the greatest public health threats of the 21st century. Indeed, infections that are untreatable due to multidrug resistance of the infected organism have become more common in clinical settings. A complete understanding of the mechanisms by which bacteria become resistant to antibiotics is of paramount importance to design novel strategies to counter the resistance threat.

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