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Bacterial Resistance in Nephrology

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Abstract **Review Article**

Bacterial resistance to antibiotics (ABR) is a major threat to public health, particularly in nephrology, with far-reaching consequences, including longer hospital stays, higher healthcare costs and increased mortality. Indeed, patients with chronic kidney disease (CKD) are a population at risk of developing infections caused by antibiotic-resistant bacteria (ARBs), given their overexposure to healthcare facilities and the quality of their gut microbiota already damaged by CKD. It is a population with very high rates of colonization and ARB infection worldwide. The mechanisms deployed by these AROs to counteract the effect of antibiotics are multiple. This may include the production of antibiotic-inhibiting enzyme (ATB), waterproofing of the bacterial membrane, or modification of the antibiotic target. They include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE) species, and several multidrug-resistant Gram-negative organisms. The emergence and global spread of these ARBs is facilitated by ATB selection pressure, inter-agency transmission of resistance determinants, suboptimal infection control practices, and frequency of international travel, among other factors. The spread of this veritable pandemic highlights the urgent need for new treatment options, the implementation of awareness campaigns to properly prescribe antibiotics and improve infection prevention practices, particularly at hemodialysis centers.

Keywords: public health, Bacterial resistance to antibiotics (ABR), nephrology, chronic kidney disease.

INTRODUCTION

Bacterial resistance to antibiotics (BRA) is a major threat to public health, with far-reaching consequences, particularly in nephrology. Patients with kidney disease, particularly chronic haemodialysis patients and kidney transplant recipients, represent a population with a high potential for developing infections caused by antibiotic-resistant bacteria (ARB). These are associated with longer hospital stays, higher healthcare costs and increased mortality, to such an extent that if drastic measures are not taken, the World Health Organisation (WHO) predicts that, within a generation, bacterial resistance will be the world's leading cause of death (10 millions deaths a year) [1]. In this review, we will take stock of the general and specific mechanisms involved in BRA, its epidemiological aspects in nephrology and the main preventive strategies for minimising both the individual and large-scale impact of BRA.

General Mechanisms of the BRA

BRA can be natural, in which case the resistance mechanism depends on the bacterium's genetic make-up and is passed on to its descendants through chromosomal inheritance. This is the case for the resistance of Klebsiella spp. to ampicillin, or that of Enterococcus spp. to cephalosporins. However, resistances that represent a real challenge from a therapeutic point of view are acquired and result either from a mutation of the bacterium's genetic heritage (chromosomal resistance), or from an acquisition of external genetic material, through plasmids from other bacteria (extra-chromosomal resistance) [2]. The mechanisms used by these ARB to counteract the effect of antibiotics (ATB) are multiple. They may involve the production of enzymes that inhibit the ATB, impermeabilisation of the bacterial membrane or modification of the ATB target. Certainly, the selection pressure of repeated ATB administration leads to the elimination of all bacteria sensitive to that ATB, allowing ARB to gain a survival advantage and thus become predominant members of the microbiota [3]. At present, there is significant variability in the scientific

literature regarding the description of ARBs. To this end, a group of international experts has suggested a classification of the various degrees of resistance. Thus, a bacterium is said to be multidrug-resistant (MDR) if it is resistant to at least one antibiotic belonging to three different classes, The advanced degrees of resistance correspond to ultradrug resistance and pan-resistance (Table I) [4].

Table I: Degree of antibiotic resistance of bacteria

Degree of resistance	Number of classes of antibiotics to which the bacteria are resistant
Multiresistance (MDR): « multidrug-resistant »	≥ 3 classes
Ultra-resistance (XDR): « extensively drug-resistant »)	All classes except one or two
Pan-resistance (PDR): « pandrug-resistant »)	All classes

BRA specific mechanisms

Gram-positive organisms

Staphylococcus aureus (S.aureus)

Antibiotics belonging to the β-lactam class interrupt the formation of the bacterial cell wall by binding to penicillin-binding proteins (PLPs). The development of β-lactam resistance by S.aureus is a constant clinical challenge. The resistance of S. aureus to penicillin was initially due to the production of penicillinas, hydrolyzing the β-lactam ring, the central structural component of β-lactams. The spread of penicillin-resistant strains was followed by the emergence of a methicillin-resistant strain of S. Aureus (MRSA) following the production of a modified PLP (PLP2a). The glycopeptide vancomycin, which inhibits bacterial cell wall synthesis, has long served as first-line option for the treatment of severe MRSA infections. However, the emergence of vancomycin-reduced susceptibility (VRSA) strains has alarmed the global community in view of the considerable therapeutic impasse; which is thought to be due to progressive adaptive changes in the bacterial wall through mutations [5, 6].

Enterococcus species (Faecalis and Faecium+++)

The development of resistance to vancomycin (VRE) by enterococci is due to the acquisition of a cluster of genes, such as vanA and vanB, which results in the synthesis of an altered cell wall peptide, preventing the binding of vancomycin to these bacteria. Alternatively, linezolid and daptomycin, lipopeptide antibiotics, have offered a rescue solution for the treatment of VRE and MRSA infections. Linezolid binds to the ribosome, inhibiting bacterial protein synthesis, while daptomycin penetrates the bacterial cell wall, disrupting cell division. However, progressive adaptive changes in the physiology of the bacterial cell wall in enterococci have led to the emergence of resistance to daptomycin and linezolid, which is of particular concern in CKD patients, where MRSA and VRE infections are common [7, 8].

Gram-negative organisms

Enterobacteriaceae

The Enterobacteriaceae family includes several bacterial genera, including Escherichia coli, Klebsiella spp., and Enterobacter spp. The BRA acquired in this family involves several processes:

• Extended spectrum β-lactamases (ESBLs)

ESBLs are mainly plasmid-mediated enzymes. They inactivate β-lactams by cleaving the β-lactam ring. These enzymes confer resistance to penicillins and many cephalosporins, including oxyimino-β-lactams (cefotaxime, ceftazidime, and ceftriaxone) but do not act against cephamycins or carbapenems, which include cefoxitin and meropenem, respectively [9].

• AmpC β-lactamases

Similar to ESBLs, AmpC β-lactamases are enzymes encoded by bacterial chromosomes but also mediated by plasmids, which increases their epidemiological risk of transmission. These are so-called derepressed high-level cephalosporinases (HLCs) that have acquired resistance to oxyimino-β-lactams. However, unlike ESBLs, AmpC enzymes hydrolyze cephamycins and are not inhibited by most β-lactamase inhibitors. SPICE organisms (Serratia, Providencia, indole-positive Proteus, Citrobacter and Enterobacter spp.) are the main producers of AmpC enzymes [10].

• Carbapenemases

These are plasmid-mediated β-lactamases that hydrolyse the carbapenem family. According to Ambler's classification, a distinction is made between class A, C and D serine carbapenemases, such as K. pneumoniae carbapenemases (KPC), which belong to class A. Metallo-β-lactamases (MBL), which are class B carbapenemases, confer resistance to all β-lactam antibiotics via zinc, with the exception of monobactams (aztreonam). Among the MBLs identified in enterobacteria are New Delhi MBL (NDM), known for its complex epidemiology, MBL imipenemases (IMP), Verona integron-encoded MBL (VIM) and Ambler class D carbapenemases of the oxacillinase type (OXA-48), which are often found in the Middle East and North Africa [11].

• Other Resistance Mechanisms

Quinolones inhibit bacterial DNA synthesis by interacting with DNA gyrase and topoisomerase IV, which modulate DNA topology during replication.

However, quinolone resistance among Enterobacteriaceae isolates is becoming more common. Typically, it occurs as a result of chromosomal mutations in genes such as gyrA and parC, encoding quinolone targets [12].

Acquired resistance to aminoglycosides is generally mediated by aminoglycoside-modifying enzymes. These are encoded by plasmids which may also include genes for resistance determinants to other antibiotics, such as KPCs or ESBLs [13]. Resistance to polymyxins (known as colistin) has also increased in recent years due to their activity against many Enterobacteriaceae isolates. Resistance is due to post-translational modifications of the polymyxin-binding target [14].

Pseudomonas aeruginosa (P.Aeruginosa)

P.aeruginosa has intrinsic resistance to many antibiotics and can acquire resistance to other classes of antibiotics. Mechanisms frequently observed in P. aeruginosa isolates include AmpC β-lactamases, ESBLs, MBLs and down-regulation of outer membrane porin D and efflux pumps [15].

Acinetobacter species

Acinetobacter spp., particularly baumannii, has been widely described for its ability to develop extensive drug resistance and cause nosocomial epidemics, especially in intensive care units; AmpC β-lactamases are intrinsically present in all A. baumannii. Acquired resistance mechanisms include MBL, OXA carbapenemases, cell wall porin mutations, and efflux pumps [16].

Epidemiological aspects of BRA in nephrology

Urinary tract infections (UTIs)

The prevalence of BRA during urinary tract infections depends on a number of factors, including residence in an area with a high prevalence of BRA, exposure to healthcare facilities, indwelling urinary catheters and abnormal anatomy of the urinary tree. In Morocco, Benhiba et al showed that Enterobacteriaceae were responsible for 88% of UTIs, 53% of which were acquired in hospitals and 47% in the community. Sensitivity studies showed a high frequency of resistance to the main families of antibiotics, with the exception of fosfomycin, nitrofurans and amikacin. Resistance to third-generation cephalosporins (C3G) through ESBL production was present in 21% of hospital strains and 11% of community strains, with high rates of co-resistance to other families of antibiotics. Finally, 2% of isolated strains were resistant to imipenem [17]. Finally, 2% of the strains isolated were resistant to imipenem [17]. Elsewhere, a study carried out in the United States, analysing the profile of Escherichia Coli (E Coli) isolated during UTIs in the general population, showed that 16.8% of patients secreted an ESBL, 21.8% of which were acquired in healthcare institutions and 14.9% in the community [18].

Dialysis-associated infections (DAIs)

• ***Hemodialysis (HD)***

The distribution of ARB related to bloodstream infections associated with haemodialysis varies considerably from one geographical region to another.

In the United States, infections reported by HD centres were related to vascular access in 76% of cases. S. aureus was the predominant pathogen (30.6%), with methicillin resistance reported in 39.5% of cases. It was followed by Gram-negative organisms (15%), particularly E. coli (17.8%), Klebsiella spp. (14.6%) and Enterobacter spp. (4.8%), which secret ESBL, cephalosporinase and carbapenemase respectively. Enterococci accounted for 5.5% of isolates, with vancomycin resistance reported in 11.5% [19].

MRSA colonisation rates in chronic haemodialysis patients range from 2.3% to 27.3% and up to 35% of colonised patients go on to develop MRSA infections within 1 year [20]. In the United States, invasive MRSA infections affect more than 4% of dialysis patients, more than 100 times the incidence observed in the general population [21]. Similar Moroccan data, published by the team at the Hassan II University Hospital in Fez, revealed that the local bacteriological profile of infections related to central venous hemodialysis catheters was dominated by S. Aureus (51.11%), which was sensitive to methicillin in all cases. Enterobacteriaceae accounted for 34.44% of isolates with resistance to penicillins, C3G and quinolones in 62.96%, 48.14% and 37.03% of cases, respectively. Seven strains of Enterobacteriaceae were secretors of extended-spectrum beta-lactamases (ESBLs) [22].

• ***Peritoneal dialysis (PD)***

Infections associated with peritoneal dialysis include PD catheter exit site infections, tunnellitis and peritonitis, which is most often caused by Gram-positive organisms such as coagulase-negative staphylococci and S. aureus.

However, a small proportion is caused by gram-negative organisms [23]. The prevalence of BRA among PD-associated infections is rising sharply and varies geographically. An Indian study of PD-associated peritonitis revealed high rates of resistance in several pathogens. Among Gram-positive organisms, almost 30% of S. aureus isolates were resistant to meticillin and 15.4% of Enterococcus isolates were resistant to vancomycin. Among enterobacteria, 54% and 76% were resistant to C3G and fluoroquinolones respectively; 11.5% of P. aeruginosa and 23.5% of Acinetobacter spp isolates were resistant to carbapenems due to MBL production [24].

Infections associated with kidney transplantation

Kidney transplant patients acquire ARB by a variety of mechanisms, including direct transmission via the transplanted organ and indirect transmission via contaminated medical equipment.Post-operative anatomical abnormalities, such as vesicoureteral reflux and ureterovesical junction stenosis, adynamic bladder and urinary diversions, may predispose transplant recipients to recurrent ARO urinary tract infections, due to repeated exposure to antibiotics and healthcare facilities [25]. The prevalence of ASR in this population varies considerably depending on the type of infection, the causative organism and the region. In Spain, 14% of kidney transplant recipients had been infected with an ARO, according to data from a prospective study carried out in a Spanish centre between 2003 and 2006. The most commonly identified AROs were E. coli, K. pneumoniae and P. aeruginosa [26].

Preventive strategies for BRA infections in nephrology

The worrying increase in BRA in CKD patients makes prevention the cornerstone of ARB infection management. There are several aspects to this:

Distinguishing between colonization and infection

A microbiological sample found for bacteria does not necessarily mean an infection. For example, a positive result of a cytobacteriological examination of the urine (ECBU) carried out "systematically" or in the presence of cloudy urine, but in the absence of any clinical symptoms (asymptomatic bacteriuria with or without leukocyturia), should not be followed by a prescription of antibiotics under any circumstances except in pregnant women or if the sample is collected from a urinary catheter before surgery on the urinary tract [1].

Prescribing antibiotics just

Over-prescription of antibiotics is due to frequent diagnostic uncertainties, often leading to "probabilistic antibiotic therapy". In addition to local bacterial ecology criteria, the site of infection and the suspected pathogen, the choice of ATB should take into account criteria inherent to renal failure, such as the need for vascular access, the potential for nephrotoxicity and dose adjustment. Each indication for the use of ATBs has a clearly defined duration, and as a general rule, the duration of treatment should be as short as possible in order to avoid the selection of resistant strains and limit the ecological impact [1].

Basic infection control measures

Preventing the spread of ARB requires strict compliance with aseptic measures, in particular hand hygiene and disinfection of surfaces and equipment, particularly in haemodialysis centres. Widespread use of hydroalcoholic solutions has proved to be a better way of limiting the hand-carried transmission of ARB, and was associated with a clear reduction in the prevalence of MRSA infections. In addition, local protocols for handling catheters in haemodialysis facilities should always be subject to regular and ongoing review. In addition, arteriovenous fistulas should be preferred to intravascular catheters wherever possible, given the high risk of infection associated with the latter [27].

Vaccination

Long used for the prevention of communicable diseases, the pneumococcal vaccine illustrates the ability of vaccines to reduce BRA, thus providing protection against antimicrobial-resistant strains, which could prove to be a promising option and an alternative for the control of ARBs [28].

Decolonization therapies

They refer to the application of antibiotic agents to suppress carriage of an organism. Approaches often used to eliminate S. aureus, and particularly MRSA, include intranasal mupirocin with or without topical antiseptics such as chlorhexidine. These decolonisation therapies have significantly reduced S. aureus infections in colonised patients undergoing peritoneal dialysis or haemodialysis. However, this has led to the emergence of resistance due to alterations in the patient's microbiome [29].

Fecal microbiota transplantation (FMT)

FMT has been explored as a potential approach to reducing antibiotic-induced dysbiosis, which increases the risk of colonisation and infection by ARB. FMT increases bacterial diversity and modifies local and/or systemic immune responses. In one study, FMT was associated with a loss of ESBL-producing Enterobacteriaceae in 20% of carriers 1 month after the first MFT, and in 40% who underwent a second F%MT following failure of the first. This suggests that this technique is potentially promising for the decolonisation of ARB and could reverse the intestinal dysbiosis predisposing patients to colonisation by ARB [30].

CONCLUSION

The growing burden of BRA is dangerously increasing the risk of infection-related morbidity and mortality. As a result, and given the vulnerability of patients with CKD, nephrologists and microbiologists need to work together to select the antibiotic treatment that will have the least impact on the microbiota of patients with renal failure, who are already weakened by their disease. Although pharmaceutical research has made it possible to propose innovative molecules in response to bacteriological developments, it remains unfortunately insufficient: new antibiotics are increasingly rare and bacteria are regaining ground, hence the vital need to develop effective prevention strategies in the hope of identifying this universal problem at the crossroads of human health.

REFERENCES

1. Hugues, C., Michael, N., & Olivier, B. (2019). When (and why) not to prescribe antibiotic therapy? *Larevuedupraticien*, 69.
2. Cristina, B., & Nicolas, T. (2016). Antibiotic resistance: the current situation in Europe and Switzerland and the impact on practitioners. *Rev Med Suisse*, 12, 1699-1702.
3. Blair, J. M., Webber, M. A., Baylay, A. J., Ogbolu, D. O., & Piddock, L. J. (2015). Molecular mechanisms of antibiotic resistance. *Nature reviews microbiology*, *13*(1), 42-51.
4. Magiorakos, A. P., Srinivasan, A., Carey, R. B., Carmeli, Y., Falagas, M. E., Giske, C. G., ... & Monnet, D. L. (2012). Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clinical microbiology and infection*, *18*(3), 268-281.
5. Barber, M. (1961). Methicillin-resistant staphylococci. *Journal of clinical pathology*, *14*(4), 385-393.
6. Walters, M. S., Eggers, P., Albrecht, V., Travis, T., Lonsway, D., Hovan, G., ... & Kallen, A. (2015). Notes from the field: Vancomycin-resistant Staphylococcus aureus—Delaware, 2015. *Morb. Mortal. Wkly. Rep*, *64*, 1056.
7. Murray, B. E. (1990). The life and times of the Enterococcus. *Clinical microbiology reviews*, *3*(1), 46-65.
8. Greene, M. H., Harris, B. D., Nesbitt, W. J., Watson, M. L., Wright, P. W., Talbot, T. R., & Nelson, G. E. (2018, October). Risk factors and outcomes associated with acquisition of daptomycin and linezolid–nonsusceptible vancomycin-resistant Enterococcus. In *Open forum infectious diseases* (Vol. 5, No. 10, p. ofy185). US: Oxford University Press.
9. Doi, Y., Iovleva, A., & Bonomo, R. A. (2017). The ecology of extended-spectrum β-lactamases (ESBLs) in the developed world. *Journal of travel medicine*, *24*(suppl_1), S44-S51.
10. Jacoby, G. A. (2009). AmpC β-lactamases. *Clinical microbiology reviews*, *22*(1), 161-182.
11. Johnson, A. P., & Woodford, N. (2013). Global spread of antibiotic resistance: the example of New Delhi metallo-β-lactamase (NDM)-mediated carbapenem resistance. *Journal of medical microbiology*, *62*(4), 499-513.
12. Aldred, K. J., Kerns, R. J., & Osheroff, N. (2014). Mechanism of quinolone action and resistance. *Biochemistry*, *53*(10), 1565-1574.
13. Doi, Y., Wachino, J. I., & Arakawa, Y. (2016). Aminoglycoside resistance: the emergence of acquired 16S ribosomal RNA methyltransferases. *Infectious Disease Clinics*, *30*(2), 523-537.
14. Baron, S., Hadjadj, L., Rolain, J. M., & Olaitan, A. O. (2016). Molecular mechanisms of polymyxin resistance: knowns and unknowns. *International journal of antimicrobial agents*, *48*(6), 583-591.
15. Pang, Z., Raudonis, R., Glick, B. R., Lin, T. J., & Cheng, Z. (2019). Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies. *Biotechnology advances*, *37*(1), 177-192.
16. Wong, D., Nielsen, T. B., Bonomo, R. A., Pantapalangkoor, P., Luna, B., & Spellberg, B. (2017). Clinical and pathophysiological overview of Acinetobacter infections: a century of challenges. *Clinical microbiology reviews*, *30*(1), 409-447.
17. Benhiba. Epidemiology and Antibiotic Resistance of Enterobacteriaceae Urinary Tract Infections in Adults at Marrakech University Hospital and Therapeutic Implications.
18. Lob, S. H., Nicolle, L. E., Hoban, D. J., Kazmierczak, K. M., Badal, R. E., & Sahm, D. F. (2016). Susceptibility patterns and ESBL rates of Escherichia coli from urinary tract infections in Canada and the United States, SMART 2010–2014. *Diagnostic microbiology and infectious disease*, *85*(4), 459-465.
19. Nguyen, D. B., Shugart, A., Lines, C., Shah, A. B., Edwards, J., Pollock, D., ... & Patel, P. R. (2017). National Healthcare Safety Network (NHSN) dialysis event surveillance report for 2014. *Clinical journal of the American Society of Nephrology: CJASN*, *12*(7), 1139-1146.
20. Zacharioudakis, I. M., Zervou, F. N., Ziakas, P. D., & Mylonakis, E. (2014). Meta-analysis of methicillin-resistant Staphylococcus aureus colonization and risk of infection in dialysis patients. *Journal of the American Society of Nephrology: JASN*, *25*(9), 2131-2141.
21. Nguyen, D. B., Lessa, F. C., Belflower, R., Mu, Y., Wise, M., Nadle, J., ... & Active Bacterial Core Surveillance (ABCs) MRSA Investigators of the Emerging Infections Program. (2013). Invasive methicillin-resistant Staphylococcus aureus infections among patients on chronic dialysis in the United States, 2005–2011. *Clinical infectious diseases*, *57*(10), 1393-1400.
22. Amir, I. Infections on hemodialysis catheters at the Hassan II University Hospital in Fez: bacterial ecology and antibiotic resistance.
23. Akoh, J. A. (2012). Peritoneal dialysis associated infections: an update on diagnosis and management. *World journal of nephrology*, *1*(4), 106-122.
24. Prasad, K. N., Singh, K., Rizwan, A., Mishra, P., Tiwari, D., Prasad, N., & Gupta, A. (2014). Microbiology and outcomes of peritonitis in northern India. *Peritoneal Dialysis International: Journal of the International Society for Peritoneal Dialysis*, *34*(2), 188.
25. Ariza-Heredia, E. J., Beam, E. N., Lesnick, T. G., Kremers, W. K., Cosio, F. G., & Razonable, R. R. (2013). Urinary tract infections in kidney transplant

recipients: role of gender, urologic abnormalities, and antimicrobial prophylaxis. *Ann Transplant*, *18*(1), 195-204.

26. Linares, L., Cervera, C., Cofán, F., Ricart, M. J., Esforzado, N., Torregrosa, V., ... & Moreno, A. (2007, September). Epidemiology and outcomes of multiple antibiotic–resistant bacterial infection in renal transplantation. In *Transplantation proceedings* (Vol. 39, No. 7, pp. 2222-2224). Elsevier.
27. Disease Control and Prevention Systems. (2001). Recommendations for Preventing Transmission of Infections in Chronic Hemodialysis Patients. MMWR Recomm. Rep 50, 1–43.
28. Von Gottberg, A., De Gouveia, L., Tempia, S., Quan, V., Meiring, S., Von Mollendorf, C., ... & Cohen, C. (2014). Effects of vaccination on invasive pneumococcal disease in South Africa. *New England Journal of Medicine*, *371*(20), 1889-1899.
29. Grothe, C., Taminato, M., Belasco, A., Sesso, R., & Barbosa, D. (2016). Prophylactic treatment of chronic renal disease in patients undergoing peritoneal dialysis and colonized by Staphylococcus aureus: a systematic review and meta-analysis. *BMC nephrology*, *17*, 1-10.
30. Hudson, L. E., Anderson, S. E., Corbett, A. H., & Lamb, T. J. (2017). Gleaning insights from fecal microbiota transplantation and probiotic studies for the rational design of combination microbial therapies. *Clinical microbiology reviews*, *30*(1), 191-231.