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EDITORIAL

Antibiotic resistance in urinary infection: the never-ending story☆

Resistencia antibiótica en la infección urinaria: la historia sin fin

For more than 60 years, antibiotics have been considered a panacea to cure bacterial infections, which is why their use has spread worldwide, although unfortunately not always in an equal or appropriate manner. Due to this situation of misuse, especially in infections that do not require antibacterial medications (viral infections), incomplete antibiotic therapy, or use of the wrong antibiotic for susceptibility of the organism, it has favored the emergence, selection and, finally, the spread of bacterial strains resistant to these therapies. This has resulted in a dangerous "weapons race" of discovery and production of new antibacterial drugs, while microorganisms do their part to develop mechanisms that prevent these drugs from being effective in eliminating them.

Alexander Fleming, who discovered penicillin, prophetically warned in his speech when receiving the Nobel Prize for Medicine in 1945 that bacteria "could become resistant" to these wonder drugs. In this context, it should be understood that the development of antibiotic resistance is a normal evolutionary process in microorganisms but it is accelerated by the pressure exerted by the widespread and often incorrect use of antibacterial drugs in humans.

A fact that should also be considered of importance is the use of antibiotics to improve agricultural production because large reservoirs of bacterial resistance in farm animals have been created.

The emergence of antibiotic-resistant bacteria can result from spontaneous chromosomal mutations that provide selective advantages and allow organisms to change the site of action (target) of the drug, increase their elimination or limit its availability within the organism. This resistance can also be acquired from foreign genetic information through transposons and plasmids, which are transferred among organisms of the same or different species. These plasmids can carry, concurrently, resistance genes to different antibiotics, creating multiple resistances. In both cases, one or more of the mechanisms of antibacterial drug attacks can be eliminated.

Undoubtedly, pharmaceuticals used against infections affecting humans have prevented the suffering and deaths of countless people and for several generations, but the economic cost of maintaining a positive balance has been increasing and, therefore, selective, so there is a need for designing a global strategy to control this menace.[1] Children, especially infants and toddlers, are more vulnerable to bacterial infections than adults, either due to their lack of immunological maturity or due to some predisposing anatomic situations and are more likely to be exposed to infectious diseases in relation to their habits and environments. It should be added that many antibiotics have not been approved for use in children. This is partly due to their metabolic differences from adults, which makes them unsafe for this age group.[2]

One of the most common bacterial infections in children is urinary tract infection (UTI), a pathology that focuses on a large variety of pathogens. In these patients, correct and early antimicrobial therapy aims to relieve symptoms, eradicate the pathogen, prevent disease progression and reduce the risk of future kidney damage. In this sense, and because the culture of the pathogen is not usually reported within 24 h, most often the choice of the antibiotic is empirical and based on epidemiological data of bacterial etiologies and the most common antibiotic susceptibilities of the region where the UTI is diagnosed.

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In this issue of *Boletín Médico Hospital Infantil de México* (*BMHIM*), López et al. present an interesting study related to the etiology and antibiotic susceptibility of uropathogens in a significant number of children affected by uncomplicated community-acquired UTI and hospitalized in México City, México. In this "epidemiological snapshot" of a geographic area, an increasingly global reality is observed: first, *Escherichia coli* is still the main organism causing UTI, but at a lesser prevalence, whereas some Gram positive and many Gram negative organisms increase proportionally; secondly, the susceptibility of many of these pathogens to antibiotics widely used as first line empirical schemes decreases.[3]

The reason for the increased antibiotic resistance to uropathogenic bacteria is multifactorial but is frequently caused by prolonged and, at times, inappropriate use of these drugs. In this regard, it is important to mention the prolonged use of chemoprophylaxis in patients with vesico-ureteral reflux, urinary malformations, neurogenic bladder, recurrent UTIs and some cases of urosepsis follow up.[1,4,5] Other associations described are the use of corticosteroids, immunosuppressive drugs and the presence of gastro/jejunostomy tube. In relation to the resistance of uropathogens in hospitalized patients, a more frequent situation, we should consider the use of broad spectrum antibiotics, prolonged hospital stay (especially in intensive care units), serious illness, abdominal surgery, ventilatory support, vascular catheters and urinary catheterization, among others.[5-7] Obviously, one can also observe infections due to these resistant organisms in patients who had not been detected to have any known risk factors. It should be kept in mind that these UTI caused by resistant pathogens generate higher healthcare costs, longer hospitalizations and significantly higher mortality.[6,8]

Without claiming to be exhaustive, it is important to note some of the uropathogens where the major problems of antibiotic resistance are concentrating. For its frequency and importance, *E. coli* is emphasized due to it being resistant to third-generation cephalosporins, especially in the presence of extended-spectrum β-lactamases (ESBLs) and resistance to quinolones. Also noteworthy is *Enterococcus* spp, especially *E. faecium*, with increasing resistance to vancomycin; *Pseudomonas aeruginosa,* resistant to quinolones and third-generation cephalosporins; and the enterobacteriaceae, *Enterobacter cloacae* and *Klebsiella pneumonia,* with multidrug resistance mediated by ESBL.[1,5-7]

As therapeutic perspectives to these powerful pathogens, new resistant drugs have been developed against the defensive mechanisms of these bacteria, whereas "old" drugs have regained susceptibility to these aggressors, as is the case with some aminoglycosides and nitrofurantoin.[6,7] Unfortunately, almost all of these new drugs do not have a formulation to be orally administered, which makes treatment of uncomplicated infections a complex issue. Furthermore, and of great future importance, strategies must be implemented to prevent infection with these multiresistant pathogens, such as barrier protection of patients infected or colonized and restricting the use of β-lactams. Public policies should also be implemented for sanitation of drinking water and food preparation because some of the antibiotic-resistant (ESBL+) agents can reach us by consumption of contaminated food and water.[6,7]

It is important to know, in an actualized form, changes in the minimum inhibitory concentrations of various antibiotics in order to define the criteria "break points" for their sensitivity. Thus, many organisms previously categorized as susceptible to some antibiotics can now be considered having intermediate or resistant susceptibility by using the above criteria.[6,9] Therefore, clinicians should periodically review local practices with their own microbiology laboratories. Moreover, we must consider that antibiotics, when concentrated in urine, can sometimes produce excellent response *in vivo*, although the uropathogen has proven this resistant *in vitro*.

With all the elements described, it becomes essential to perform periodic assessment, ideally annually, of the prevalence and antimicrobial resistance of the most common uropathogens in each healthcare institution or health area as described in this issue of *BMHIM*, thus implementing regional monitoring networks for antimicrobial susceptibility as suggested by the WHO.[1,3,10]

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